

The American Journal of **DIGESTIVE DISEASES**

An Independent Publication

DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

ORIGINAL CONTRIBUTIONS

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2. Wooldridge, W. E. and Mast, G. W.: Am. J. Surg. 78:881.
3. Swalm, W. A.: M. Rec. 140:26.

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*Average number of calories and average amounts of the chief nutrients furnished by six-ounce servings of cooked meat (averages of amounts furnished by six ounces each of cooked beef, lamb, pork, and veal).²

†National Research Council's recommended daily allowances for a sedentary man (154 lb.).

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1. King, C. G.: Trends in the Science of Food and Its Relation to Life and Health, Nutrition Rev. 10:1 (Jan.) 1952.
2. Watt, B. K., and Merrill, A. L.: Composition of Foods—Raw, Processed, Prepared, in Agriculture Handbook No. 8, United States Department of Agriculture, Bureau of Human Nutrition and Home Economics, 1950.

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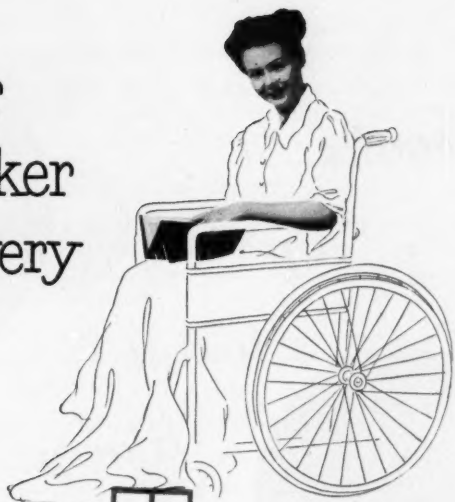
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*Spies, T. D.: Rehabilitation Through Better Nutrition, Philadelphia, W. B. Saunders Co., 1947, p. 62.

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¹ Rollins, C. T., to be published.

² Joslin, C. L., Del. St. Med. J. **25**:35, 1950.

³ Quintos, F. N., Philippine J. of Med. **26**:155, 1950.

⁴ Fitzpatrick, V. P., Hunter, R. E., and Brambel, C. E., Am. J. Diges. Dis. **10**:340, 1951.

⁵ Meyer, K., Prudden, J. F., Lehman, W. L. and Steinberg, A., Am. J. Med. **5**:482, 1948.

⁶ Martin, G. J., Am. J. Diges. Dis. **18**:16, 1951.

⁷ Moss, J. N. and Martin, G. J., Am. J. Diges. Dis. **15**:412, 1948.



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RELATIONSHIP BETWEEN HISTOLOGICAL LESIONS AND RADIOLOGICAL SIGNS OF CANCERS OF THE MUCOUS MEMBRANE OF THE STOMACH

(CANCERS LOCALIZED IN THE MUCOUS MEMBRANE AND NOT HAVING SPREAD TO THE WALL: STAGE I)

GUY ALBOT* AND JACQUES TOULET,** Paris, France.

THE AIM OF OUR work has not been to exhaust the numerous problems raised by the early diagnosis of gastric cancer, but simply to reveal the anatomical substratum of the initial radiological signs of this cancer.

During the past twenty-five years French works on this subject have considerably increased following R. A. Gutmann's research which has at last enabled an early and regular diagnosis of gastric cancer to be made. (1, 2).

Between 1932 and 1938, R. A. Gutmann established a distinction between the radiological aspects suggestive of cancer (infiltrated condition, tapering of the pylorus, recessed condition, recessed niches, niches in an arch-shaped space and plateau-shaped niches) and above all, he introduced the main idea which dominates the history of the early diagnosis of cancer: his radioclinical method and his therapeutic test alone, in the case of suggestive radiological signs, enable a sure diagnosis to be made (1).

It is only by the comparison of numerous perfect exposures in different positions (standing and in a pro-cumbent posture), taken in series, and especially by the repetition of these examinations at intervals of from three to six weeks, separated by an active treatment (mainly shock treatment) that the benignity or malignancy can be diagnosed according to the reduction, the persistence or the increase of radiological lesions, along with the modification of the clinical elements.

It is on this basis that the French school has continued to work for twenty years, giving details of suggestive radiological aspects of organo-functional images and purely spasmodic elements, studying the modifications of the perilesional mucous relief (Guy Albot), showing in detail the results of pharmacoradiography in the study of incipient cancer (G. Albot) and proving the great value of R. A. Gutmann's radioclinical method.

In order to put into practice the radioclinical method of gastric cancer diagnosis, it is first of all necessary to have located one of the "suspicious" radiological aspects. As their anatomo-pathological substratum is still little known, we thought it useful to define it as a result of 277 personal observations of gastric cancers diagnosed and operated upon in their incipient stages.

*Head of gastro-enterological department, Saint Antoine's Hospital, Paris. Home address: 202, bvd Saint-Germain, Paris 7e.

**Former head of Clinique of the Faculty of Medicine, Paris. Assistant Doctor in gastro-enterology at Saint-Antoine's Hospital.

Submitted Nov. 27, 1951.

A perfect knowledge of histological lesions which are at the base of every tell-tale radiological aspect and the understanding of the mechanism by which they induce it can alone enable us to understand why this condition is suggestive of cancer, why and under what conditions certain non-cancerous lesions may give rise to it. This fuller understanding of the mechanism of these signs will obviate possible mistakes and will help the gastroenterologist in the difficult task of locating an incipient cancer (14).

The study which we give today will be restricted to the radiological signs of cancers of the mucous membrane which constitute the most difficult histological problem. We shall confine ourselves to emphasizing the differences which may, from this point of view, separate the mucous membrane stage from other stages of gastric cancer.

DIFFERENT STAGES OF CANCER OF THE STOMACH

There have been numerous discussions in France on the subject of the duration of the histological stages of gastric cancer. These are outside our province and we shall not consider them here.

We shall be content to define our subject clearly, using the international nomenclature.

Cancer in situ (stage 0), corresponds with lesions made up of simple intraglandular cellular irregularity, without any rupture of the basic membrane. The rarity of such observations will be appreciated; they form ex-

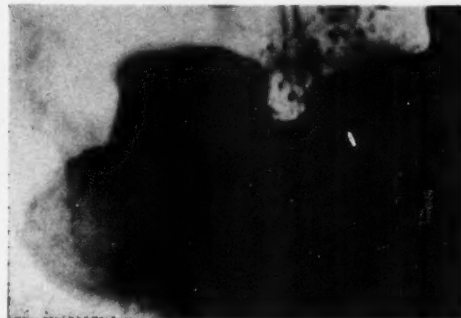


Fig. 1: M.H.U., Mareel; (Gastro-enterological Society Paris, 7 August 1944 in Arch. mal. app. dig.). *Cancer of the mucous membrane of the prepyloric antrum* revealed by a recessed condition with a rigid base of the lesser curvature, situated about 1 cm along the pyloric canal. Elsewhere functional tapering of the antrum.

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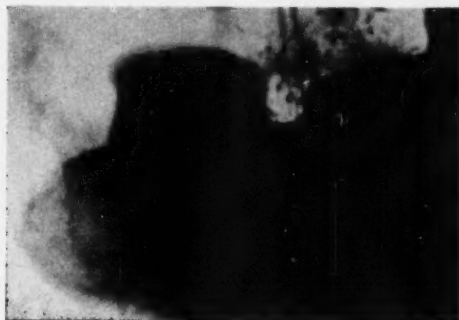


Fig. 1: M.H.U., Marcel; (Gastro-enterological Society Paris, 7 August 1944 in Arch. mal. app. dig.). Cancer of the mucous membrane of the prepyloric antrum revealed by a recessed condition with a rigid base of the lesser curvature, situated about 1 cm along the pyloric canal. Elsewhere functional tapering of the antrum.

ceptions of which it is not at present possible to make a coherent semiological study.

Cancer of the mucous membrane (stage 1), corresponds with a well-known epitheliomatous process accompanied by disturbance of the glandular architecture and spreading to the chorion, without the lesions going beyond the muscularis mucosae. It is the historadiological study of these cancers of the mucous membrane which will be dealt with here.

Incipient sub-mucosal cancer (stage 2), corresponds with very small cancer having already spread to a limited sub-mucosal segment but not reaching the muscularis mucosae and not affecting the ganglions.

Parietal gastric cancer (stage 3) constitutes a common gastric cancer with a pronounced attack on the wall and spreading to the ganglions and further afield.

The anatomical substratum of symptoms of gastric cancers varies according to the stage under consideration, and from an anatomico-radiological point of view, what is true in the case of parietal cancer is not always true in the case of cancer of the mucous membrane.

ANATOMICAL SUBSTRATUM OF RADIOLOGICAL SIGNS OF CANCER OF THE MUCCOUS MEMBRANE

If there exists a well-established notion of the parietal stage of cancer of the stomach, it is the close relationship between the infiltrated lesions and the rigidity, between the ulcerated forms and the niches, between the vegetating forms and the lacunae. This notion which constitutes the anatomico-radiological basis of the diagnosis of ordinary cancer of the stomach, loses all value as far as cancer of the mucous membrane is concerned. In the latter, we shall see the importance



Fig. 2: M.H.U., Marcel—operative specimen, Pylorus on the left. The specimen was opened along the greater curvature. The cancerous mucous membrane is slightly depressed and is situated on the front side. It rests on an infiltration up to which come the folds of the normal mucous membrane and notably a large fold of benign hyperplasia. The mucous membrane of the posterior face and of the greater curvature is retracted towards the cancer; its folds are fixed and converge towards the mucous membrane and the stomach substance is clearly contracted at this level.

of the functional or organo-functional aspects of reactional histological non-cancerous lesions and we shall show that there exist infiltrated radiological aspects without neoplastic infiltration, niches without ulceration, lacunae without neoplastic vegetation or ulcerated forms without the radiological existence of niches.

It is therefore advisable to take up again from the start the study of the anatomical substratum of radiological anomalies of cancer of the gastric mucous membrane without expecting to find there what it is usual to find in the cancer at its peak period.

This study will have the credit of removing certain very understandable reserves. For an inquiring mind, but one which is insufficiently conversant with the study of incipient cancer of the stomach, it is shocking to hear that a tumor which remains localized in an upper region of an organ, which may be imperceptible to the eye and to palpation of the operator specimen and which can only be discovered with any certainty by an histological examination gives radiological modifications of the profile of the stomach, visible to the eye and likely to allow it to be located. It would be possible to admit this in incipient cancer at the sub-mucosal stage (stage 2) since they already reach a certain depth and cover a certain though limited area; but in cancer of the mucous membrane it is difficult to realize that such minute anatomical lesions should be accompanied by such suggestive radiological aspects. It will be realized how tempting it is to doubt, *ipso facto* the value of radiological signs of incipient cancer and to resolve this difficult problem by a politely skeptical attitude, as has been seen in France and as is still sometimes seen abroad.

We have tried to present the solution to this problem. The close comparison of anatomical lesions and radiological signs actually enables a rational explanation to be made of this apparent contradiction.*

According to whether the cancer of the mucous membrane is ulcerated or not, the anatomo-radiological problem is somewhat different. So, we shall treat in turn the anatomical substratum of symptoms of cancer of

*We shall only give 2 examples to illustrate our study; the reader will find others in a previous article, c.f. ref. 14.

the mucous membrane without ulceration and that of ulceriform cancers of the mucous membrane. This distinction has only a strictly semiological value. Actually, the fact that at the mucous membrane stage a gastric cancer is ulceriform or, on the contrary, non-ulcerated, does not enable the later development of the cancer to be predicted in the event of a diagnosis not being made: this evolution may take place in the usual manner of common cancer: infiltrating form, ulcerous form, vegetating form.

I. HISTO-RADIOLOGY OF NON-ULCERATED CANCER OF THE MUCOUS MEMBRANE.

At this stage and in this form, the epithelioma forms a thin layer of epitheliomatous cells which have spread to the chorion of the mucous membrane. The region of the cancerous mucous membrane is in general thinner than the normal mucous membrane; it is sometimes irregular with atrophic zones and hypertrophic zones. At this stage the underlying cancerous infiltration is absent and ulceration and vegetation likewise: the radiological images can not therefore be in any way under the direct dependence of the epitheliomatous lesion.

These cancers of the mucous membrane are however shown radiologically by rigidities, by niches, by modifications of the profile of the perilesional mucous membrane and very often the three symptoms are associated. Actually, these radiological images simply reveal accompanying lesions: sclerosis of the sub-mucosa, reduction in thickness of the mucous membrane, retractile or spasmodic modifications of the profile of the mucous membrane around the lesion. However they are indirectly related to the presence of the epitheliomatous lesion of the mucous membrane: in fact the accompanying lesions are produced by the epithelioma and maintained by it. Radiological diagnosis of these accompanying lesions consists essentially of diagnosing radiologically the causal epithelioma: both persist and are aggravated despite the therapeutic test which enables the radioclinical method to diagnose cancer by deduction.

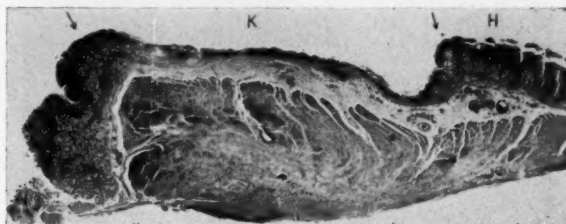


Fig. 3: M.H.U., Marcel—Overall histological aspect. The rigidity and the recessing are not due to cancer but to the fibrous thickening of the sub-mucosa.

From left to right: duodenum, pylorus and beginning of the horizontal portion of the stomach. The atrophic cancerous mucous membrane stops short on the left of the duodenal type of mucous membrane and on the right of a large fold of hyperplastic mucous membrane. Reduced to a thin cellular layer, it is not possible for it to cause the recess. The latter is the result of the important inflammatory and sclerous congestive reaction of the sub-mucosa. Note the integrity of the muscularis mucosa.

1/ *Rigidities* (infiltrated-recessed-undulating condition-tapering of the pylorus).

Since the cancer has not attacked the wall, it can not explain the rigidity. This is conditioned by a considerable sclerosis and by a congestive reaction which thickens the sub-mucosa over an area appreciably greater than that of histological cancerization of the mucous membrane.

In the *recessed condition*, the greater sclerous thickening of the wall is enough to explain the depression at the bottom of which the recessed rigidity is situated, accessorially a contraction of the muscularis mucosa may add its effect to the sclerous factor in producing the radiological image. Figure I (Mr. HU . . . Marcel) clearly reveals the origin of such a recessed condition on the prepyloric region. This patient had suffered from periodical epigastric cramps for 4 years when we examined him. A recessed condition of the lesser prepyloric curvature (fig. 1) persisting in spite of the therapeutic test, and an organo-functional tapering of the antrum prompted the operation which allowed an epithelioma of the mucous membrane to be removed (fig. 2). The recessed condition was due to the contrast between a fibrous sub-cancerous pastille and the

neighboring hyperplastic and supple mucous membrane (fig. 3). The tapering condition of the antrum was caused by the retraction of supple tissues in the direction of a slight sclerous lesion which was situated on the front side of the lesser prepyloric curvature.

In the *undulating condition* the thickening of the sub-mucosa, is apparently of different consistency according to the extent; but the anatomical substratum is identical.

Finally the *taperings of the pylorus* are also conditioned by the sclerosis but depend on a rather special mechanism. Sometimes the sclerosis is extensive and concentric, thus narrowing the aperture of the prepyloric antrum. Most frequently however, the sclerosis is not circular but retractile and thereby causes early organo-functional deformations in this narrow region which are an excellent indication of cancer.

2/ *Niches without ulceration* (ordinary niches or plateau-shaped niches of the mucous membrane, recessed niches, niches of the mucous membrane in an arc-shaped space).

With mucous cancers *niches can be observed immediately* although the cancer shows neither ulceration nor exulceration. These niches, independent of any



Fig. 4: M. R. A. F., Léon—(unpublished observation). Epithelioma of the gastric mucous membrane of the prepyloric antrum complicated by peptic ulceration. The lesser, immediately prepyloric, curvature is the centre of an almost rigid stiffening in the centre of which rises a typical long, shallow, plateau-shaped niche which was constant on all negatives in several series of radiographies. Elsewhere, the insertion of the pyloric canal is eccentric.

loss of substance, are dependent on several factors which furthermore may be combined.

Abrasion of the epitheliomatous mucous membrane which is always present, seems to be the most important of these factors. The cancerous mucous membrane remains devoid of glandular elements over all the corresponding surface and because of this presents an extremely marked attenuation. On the operatory specimen one has the impression of a hollow, a fairly deep and wide depression whose filling by baryta may explain the spontaneous image of the niche. (c.f. 14 fig. 5, 6, 7, 8).

In other cases the depression is insufficient to explain the formation of the niche. It would appear then to be a question of the *contraction of the muscularis mucosae* around a very limited and slightly rigid lesion. The irritation provoked by this lesion and by the accompanying sclerosis would explain the maintenance of the muscular fibers in a state of tension. This interpretation had already been proposed by R. A. Gut-

mann who pointed out that, because of this fact, the lesion is as it were "worn" in a permanent fashion on the outside by a kind of contraction.

Most frequently in the case of these spontaneous niches without ulceration the two mechanisms we have just mentioned are associated. Also associated with this is a localized sub-mucosal sclerosis which is responsible for the flat and rigid bottom of the plateau-shaped niches.

As well as spontaneous niches without ulceration, cases may be observed in which the niche only appears when induced by pharmacoradiography (8, 9, 10, 12, 13). From a semiological point of view these cases are very interesting; they are even more so from a dogmatic point of view as they prove the contraction of the muscularis mucosae which up to the present time was only suspected.

Whilst in the preceding cases the abrasion of the mucous membrane and the contraction of the muscularis mucosae were sufficiently marked for them to

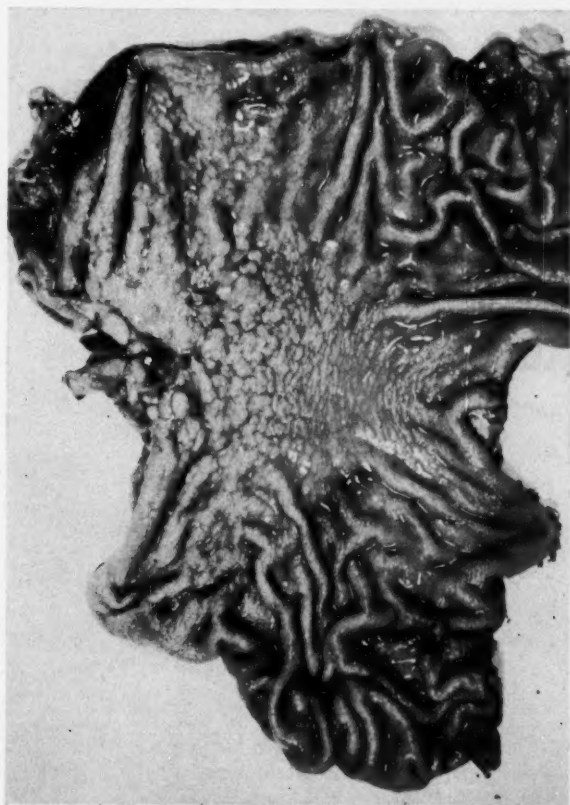


Fig. 5: M.RAF., Léon—operatory specimen—pylorus on the left.
The specimen was opened along the greater curvature; immediately before the pylorus there is a depression of the mucous membrane surrounded by several protruding buds of mucous hyperplasia.

be revealed spontaneously by the image of a niche, it may happen that, being weaker, they pass unnoticed at first but are easily "potentialized" by a pharmacodynamic stimulus such as morphine or insulin. We have already given an example of this in a previous article devoted to pharmaco-radiography (ref. 3, fig. 6): where there existed only a slightly rigid or recessed zone before, pharmaco-radiography by venous injection of morphine caused a typical plateau-shaped niche to appear whose formation can only be understood by a contraction of the muscularis mucosae due to morphine.

3 *Modifications of the perilesional profile of the mucous membrane*: converging folds finish at a distance with abnormal club-shaped endings; invariable and fixed perilesional folds.

All these characteristics are inconstant and subsidiary. However when they exist, they enable a suspicion of cancer to be verified. Their appearance is sometimes provoked by pharmaco-radiography and this in certain cases may induce elsewhere very marked autoplasmic movements of the mucous membrane which are accompanied by modifications in the disposition of the folds. But these modifications are only to be seen in the distal extremity of the folds, their proximal extremity remains invariable with its abnormal ending swollen in the shape of a club (II).

This invariability of the folds around the lesion and their club-shaped appearance are induced partly by sub-cancerous retractile sclerosis and partly by the contraction of the muscularis mucosae which morphine accentuates.

There again we find the action of the epithelioma by means of the interposed lesion on suspected radiological modifications.

The study of these four cases of non-ulcerated cancers of the mucous membrane chosen from among many others yields a lot of useful information which we shall enumerate by way of conclusion.

In cancer of the mucous membrane, the radiological signs do not depend directly on the neoplastic lesions. Actually it is no exaggeration to affirm that *at this stage, diagnosis of cancer is founded on symptoms whose immediate anatomical substratum has nothing really cancerous.*

But in practice it is just as though the cancer itself were responsible for the radiological modifications. Sclerosis, congestion, spasm of the muscularis mucosae develop, and similarly during the therapeutic test the radiological modifications continue and are aggravated. These characteristics mark the contrast between radiological modifications and similar modifications likely to be induced by benign lesions, ulcers or chronic gastritis, which may be influenced by the therapeutic test.

II. HISTO-RADIOLOGY OF ULCERATED CANCERS OF THE MUCOUS MEMBRANE

The cancerous mucous membrane can undergo peptic digestion and give rise to ulcerations of variable depths: erosion or ulceration of the muscular coat. But, in this variety, whatever the intensity of the peptic digestive process, only the edges of the ulceration are neoplastic and the cancer itself remains strictly mucous.

We shall not deal here with the secondarily transformed benign ulcers, but only with ulceriform cancers of the mucous membrane whose genesis follows the process we have just indicated.

The histo-radiological similarities vary in these forms according to the progress of peptic digestion. As the



Fig. 6: M.HU., Marcel. Overall histological aspect. The rigidity and recess are not due to the cancer but to the fibrous thickening of the sub-mucosa. The plateau-shaped niche owes its form to the extensive and shallow nature of the peptic ulceration which is itself conditioned partly by the fragility of the epitheliomatous mucous membrane and partly by the solidity of the sub-mucosal sclerosis.

From left to right: duodenum, pylorus and beginning of the horizontal portion of the stomach. The cancerous mucous membrane is exulcerated towards the centre of the lesion and replaced by a fibrinous padding. At this level there is no epitheliomatous tissue. The cancer is only shown by the edges of the ulceration and at this level it does not go beyond the muscularis mucosa. The sub-mucosa is considerably thickened, congested and infiltrated at certain points with some mononuclei; it is not attacked by the epithelioma.

latter progresses the anatomical ulceration increases in importance and its moulding by baryta causes radiological niches to appear with increasing speed.

But the cancer still remains confined to the mucous membrane. Thus the niche only represents the moulding of a peptic ulceration not specifically cancerous and the characteristics of malignancy (persistence of the niche, rigidity localized round the niche, flat depression of Ackerlund, increase in the niche recess, appearance of a minute niche in an arc-shaped space underneath the niche) remain dependent on the reactional phenomena, on sclerosis, on congestion as in the preceding variety.

In short, the ulcerated cancer of the mucous membrane forms a histo-radiological picture in which can be distinguished the elements of cancer of the mucous membrane without ulceration to which is added an ulcerous niche due to peptic digestion of the cancerous mucous membrane.

According to the extent of peptic digestion, a common niche or a plateau-shaped niche will be seen to appear; we shall also see that certain ulcerations do not cause a niche, a fact which shows that the functional phenomena and the muscular contractions of the muscularis mucosae continue to play quite an important rôle there also.

1. Common niches; common niches on a rigid base, recessed niches or niches in lacuna.

The appearance of a process of peptic digestion, clearly localized at the level of a cancerous mucous membrane which is already accompanied by extensive congestion and sub-mucosal sclerosis, will reveal the well-known aspect of the common recessed niche or of the niche in an arc-shaped space. This niche could not be otherwise than common since it results, as in the

case of benign ulcer, from digestion of the mucous membrane of the stomach. However, in this case, as in the preceding ones, the suggestive symptoms such as rigidity and formation of a recess will here again depend on secondary processes, on sclerosis in particular.

In section, the epitheliomatous mucous membrane is abraded, the corresponding sub-mucosa is sclerous, the muscularis is drawn towards the base of the ulceration and its fibres are clearly dissociated by a marked sclerous transformation which practically breaks the muscular layer. Everything occurs here as if it were a cancer of the mucous membrane complicated locally by a small peptic ulceration (ref. 14).

2. Simple plateau-shaped niche, recessed or in a lacuna.

It is sufficient for this peptic ulceration to have a large surface area though only superficial for there to be a plateau-shaped niche. Here again, according to the case in point, the importance of the sclerosis which accompanies cancer of the mucous membrane will enable the different manifestations of the niche plateau-shaped, recessed or in a lacuna to be appreciated.

If the plateau-shaped niche is generally more likely to be cancerous than the niche of ordinary appearance, that is easily understood from the fact which we have examined above. Actually cancer of the mucous membrane is accompanied by a thick, solid and extensive sub-mucosal sclerosis; the peptic ulceration will have a tendency to attack a wide area of mucous membrane weakened by its epitheliomatous degeneration, but will only be slightly inclined to bore deeply. That is why, in the beginning, ulcerations will have this extended form of the plateau-shaped niche.

Fig. 4 shows in the case of a patient of 54 (M. RAF., Léon), 10 months after the onset of pain, a plateau-

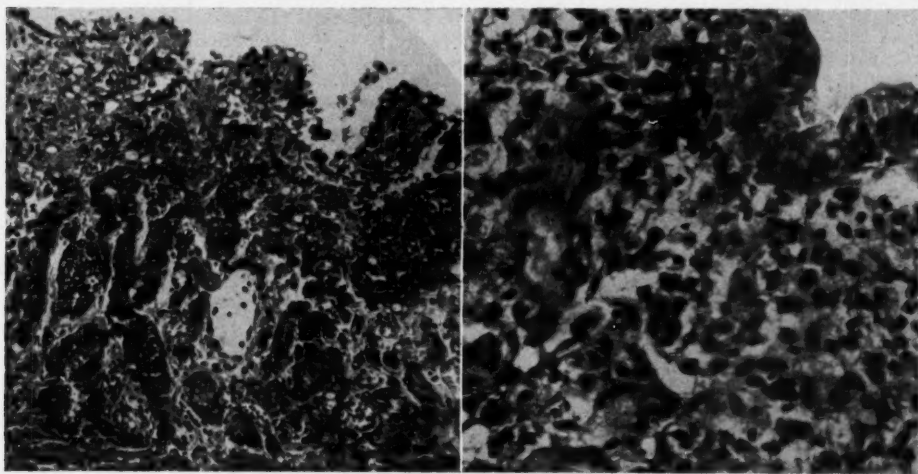


Fig. 7, A and B: Histological aspects of the two cancers of the mucous membrane given here as example. On the left, M.HU., Marcel. Trabecular epithelioma (at other points in the mucous membrane there were found mucoid conditions and infiltrating atypical conditions). On the right, M.RAF., Leon. Mucoid epithelioma with undifferentiated epitheliomatous cells and ring cells.

shaped niche of the lesser prepyloric curvature resting on a rigid base which extends beyond it on both sides. The surgical specimen (fig. 5) showed a prepyloric depression which histologically encroached a little on the sub-mucosa (fig. 6); but it was a case of superficial non-cancerous peptic ulceration, the epithelioma, of a mucoid type (fig. 7 on the right) remained localized at the mucous membrane on both sides of the ulceration. The rigidity was accounted for by a serious fibrosis of the sub-mucosa (fig. 6).

3. Ulceration without niche.

The loss of substance caused by peptic digestion of the cancerous mucous membrane is not however always sufficient to explain the origin of the niches. It is very likely that, as with niches without ulceration of non-ulcerated cancers of the mucous membrane, there exists a functional factor represented by the contraction of the muscularis mucosae which causes a sort of well with the ulcerated lesion at the bottom.

The proof of this lies in the cases of ulcerated cancer of the mucous membrane in which, even with the use of pharmaco-radiography, the niches can not be brought to light, and which show clearly the inconstancy of the perilesional functional reactions.

Such cases show that it is illusory to try to draw certain diagnostic conclusions from as close an analysis as possible of the characteristics of the different varieties of ulcerations. It is wiser not to force conclusions but to be satisfied with discovering conditions suggestive of cancer and submitting them to a well-conducted radiological therapeutic test while realizing that very often the study of anatomical lesions will reveal a relative error in over-estimating or under-estimating the extent or the depth of lesions.

In short, all that was said in connection with non-ulcerated cancers of the mucous membrane may well be applied to the same cancers when they are ulcerated. There is one point of difference: the niche is generally more important, often super-imposable on all the negatives because a peptic ulceration is of preponderant importance in its genesis. However this factor is not unique since we have seen that there may exist ulcerated forms without it being possible to find a niche.

CONCLUSION

The comparison of radiological signs and of lesions of gastric cancers at different stages allows a different anatomical substratum to be assigned to the radiological images according to the degree of evolution.

At its highest point, the radiological image is, evidently, and as it is usual to consider it, closely connected with the cancerous lesion. The rigid conditions show a neoplastic infiltration, the aspects of the niches a neoplastic ulceration, and the aspects of lacuna a neoplastic vegetation.

At the incipient sub-mucosal cancer stage, the radiological image does not at all reveal the cancerous lesion but only the reactional modifications of the sub-mucosa, which greatly exceed in area the often tiny mucous lesion which gave rise to them: sclerosis, contractions of the muscularis mucosae, edematous and inflammatory infiltrations, functional modifications of the perilesional mucous profile. Their evolution has been followed by the radioclinical method and in the course

of the radioclinical therapeutic test; as they are directly influenced by the epitheliomatous transformation of the corresponding mucous membrane it all comes about as if the radiological anomalies were the direct consequence of the cancerous lesion.

These facts deserve to be known as they explain certain surprising details in the radioclinical study of suspected cases of incipient cancer of the stomach on which we have laid stress (4, 5, 6, 7, 11, 15).

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WHY NOT BETTER TYPES OF STOOL EXAMINATIONS?

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IT IS A different thing to have solved the etiology of an infectious disease by discovering the micro-organism that causes it, than to explain the chemical, catabolic and cytological changes of the many non-infectious conditions that affect the human body. In these obscure chemical and cytologic conditions there are myriads of different cell reactions and changes in biologic substances, many of which cause functional and organic diseases of the body. We know of many chemical items that have to do with the processes of life, but how they are related with one another will remain a mystery for many years to come. In the knowledge of disease and disorder production we have hardly scratched the surface of body chemistry and biology, and pretty much all of the components of life and living are almost completely hidden from us. While being debated, there is sufficient basis for the assumption that in biotoxic intestinal states one can see the presence of certain clinical states. In part of a broad field of clinical medicine for instance one can see the frequency of gallbladder, liver, vascular, hypertensive, nervous states, etc. in the acid fermentative intestinal disorders, and the debilities, anemias, neurologic states etc. in the putrefactive disorders not to mention the multiplicity of general body functional and gastro-intestinal disorders that may exist alone or accompany definite clinical states. Not until these obscure conditions can be eliminated should the present psychiatric popularity be received with the attention and interest that is being given it. The profession is short sighted indeed to react quickly to psychiatric attitudes and procedures to explain things that are not organic, malignant or infective as due only to personality or environmental conditions. Abnormal chemical states and changes in cell function are common in biotoxic conditions, which if benefited would change the whole psychology of the individual. It can honestly be said that but very few individuals should be submitted to psychiatric handling on the presumption that nothing is corporally wrong unless as complete a biological study as possible had been made. It is my belief that these chemical disorders are far more important in producing complaints than all the organic, malignant, infectious and psychiatric disorders put together.

There are only three sources of entrance into the human body, the digestive and respiratory tract and skin, and of these the digestive tract is by far the most important. On the absorptions from this tract, practically the entire body chemistry depends. Against many of these inimical substances, conjugating substances are constantly operating to neutralize them, but in the broad field of clinical medicine it can be proven that conjugations are not always at a 100 per cent efficiency and no doubt for some of the exogenous infections no conjugations exist. Chemical substances could cause changes and many of these are not being possible to discern or estimate by any of the known methods of examinations. The statement is not justified that the chemical and micro-organism content of the intestinal

canal is of no significance clinically, even if direct proof of it does not exist. One notes this expression far too often. A further criticism is that a high incidence of pathologic or zymogenic micro-organisms in stools is only a secondary infection matter and of no importance. One is not justified in the belief that because the bacterial examination of stools is so difficult that the proper attitude to take is that it is of no clinical value. Another source of criticism is that intestinal organisms are subject to changes by diets, but one must remember that being facultative the most important of intestinal organisms usually become operative again on opposite types of diet in a very short time. Opposite types of diet may modify for a short time but no diet can influence or destroy the genus type of organism. It has also been debated that mutability of one organism into another makes the work of careful stool examinations of dubious importance. Mutability of these organisms is of very minor importance if it occurs at all. In different environments organisms may change morphologically and culture wise and sometimes even in staining characteristics, but the same genus types remain and the changing of an organism into some other type is impossible.

The average stool examination as done today is much of a useless sort of thing. Many physicians do not engage in it at all, some test only for the presence of blood, others may include a quick examination for food detritus or ova, and occasionally a Gram differential stained slide of feces is deducted from as to the bacteriologic contents. Those things like reaction, color and character that put the smallest test on the unpleasantness of working with feces is usually mentioned. In the acute diarrhetic states (B. dysentericus, salmonella, cholera, typhoid, etc., infections) special request usually brings about a worthwhile examination for these specific infections, but concerning stool examinations as carried out by private and hospital laboratories, the less said about their usefulness the better. And yet there is a tremendous wealth of clinical suggestion that may be gleaned from a proper examination of feces. The proper examination should also comprise suggestion of the following items of interest and procedure. It is not the purpose of this article to present all there is about stool and urine examinations. Only a few high lights are mentioned to encourage more complete findings. These may be mentioned as:

COLOR

Light yellow is often due to bacterial reduction of bile pigment and this usually is due to an upper level small intestinal enteritis, jaundice states, or the ingestion of excessive starch. Clay-colored stool is common in excess fat and bile obstruction. Greenish yellow gassy stools characterize fermentative biotoxic states and commonly denote an anaerobic infection. Dark stools are seen in hemorrhage from above sigmoid and due to hematin and definitely tarry stools are usually due to

upper level bleeding. Slight blood mixed with mucus may be present in invagination and polyposis, and mixed with pus in the dysenteries. Excess mucus is seen in allergies, and in neurotic gut conditions. The very dark scybalous stools are noted in colonic stagnation, and biotoxic states of the mixed or putrefactive types.

REACTION

While this is conditioned by diet, it must be remembered that the reaction of normal stools is neutral (amphoteric). With changes in the bacteriology it is acid in the fermentative toxemias due to butyric, acetic, propionic, valeric and other organic acids and generally to split down products in sequential changes between different micro-organisms. The opposite is true in the putrefactive states where alkalinity prevails due to ammonia and other products of an alkaline nature mainly those of the ptomaine or cadaverous order. Here of course resorption of sulphur compounds, mercaptan, hydrogen sulphide, and putrefaction products generally accomplished their effects in bringing on physiological perversions, organic disease and a broad expanse of functional disturbances and complaints. An essentially neutral reaction in the mixed toxemias is most confusing and in this instance one must depend on the other findings for diagnosis.

Complements of abnormal feces are the urine findings of indican, (protein putrefaction), uroscopin and oxalic acid (carbohydrate fermentation) and evidence of kidney irritability. Highly acid urines and the excretion of phenol-potassium sulphate suggests colonic disorder.

FORM

Other than diarrheal conditions, the form of stools has significance. The scybala (goat-droppings) type is characteristic of constipation, and the ribbon and pencil type indicative of spasm from toxemia, allergy or a low degree of congestive irritation—usually seen in neurotic individuals. The stools in aciduric fermentative conditions are usually mushy, greenish-yellow and filled with small collections of gas and there rarely is constipation.

A fairly accurate diagnosis of biotoxic states can often be made from the appearance, reaction, and color of stools plus the urine findings.

FOODS

Undigested food particles give much information. One sees large undigested food particles (usually meat) in achylia, pernicious anemia, diarrheal conditions and irritative bowel states. Excess fat, fatty acids and fatty soaps are seen in pancreatic conditions, and deficiency of biliary function. Knowledge of the appearance of foods under low power is necessary to learn and become familiar with, for many times vegetable cells are mistaken for ova. The importance of meat fibers should be judged, and the same may be said of mucus (incorporated and on the surface).

Other findings of importance are leucocytes, pus, erythrocytes, crystals (triple phosphate in chronic enteritis and calcium oxalate in deficient vegetable digestion).

PARASITES

The examination for parasites and ova is very poorly done in an average way. Often these are missed entirely, the ova are misnamed or macrophages or vegetable cells are judged as ova. Considerable experience and careful searching with good technique of preparation of the specimen are essential for this work. There is a belief that unless there are symptoms of irritation of the colon present (diarrhea) no significance should be placed on the presence of parasites. A careful history of these people strongly suggests that this is only seldom true. It is accepted that the nematodes are always important from a clinical standpoint. Mistakes are made in the ova of ascaris in judging these to be vegetable cells and vice versa, and confusion incident to different appearance of the fertilized and the non-fertilized forms is common. Since the adult worm is but rarely passed this changing of the ova is important. The oxyuris enters no problem and the lamblia and the strongyloides occasionally are responsible for a persistent diarrhea. Today and especially in our northern countries the ova of hook worms are practically not reported and yet are occasionally met with. The tape worm parasites generally offer no problem.

Of much importance are the amebic infections. Of the six common types of ameba that infect man it is supposed that only the histolytica is important. Practically however, they all possess the faculty of bringing about parasitic effects on the micro-organisms then present in the intestinal canal and these are occasionally important clinically in an indirect way. That is the reason that parasites should be carefully searched for and removed before significances in other directions are made. In a biotoxic gut state to leave parasites dwelling in the colon obviates the result from treatment. When present in vegetative form the endameba histolytica are not difficult to see in the fresh specimen. However, knowledge of the appearance of the other forms of ameba is essential for accurate diagnosis. Since the cystic forms are mostly studied, great care should be employed that mistakes do not take place. In the instance of chronic carriers it will be observed that this nonpathogenic type of endameba histolytica belongs to the small form, probably kept that way by certain form of *B. Coli*. Since it is very probable that a status of bacteriology is a necessary part of amebiasis, it is desirable after the ameba have been eliminated that bacterial studies are made to explain persistent symptoms (diarrhea and irritation).

I have yet to see mention made of *balantidium coli* as a cause of colon irritation, ulceration and hemorrhage, and yet I have met with this infestation four times.

BACTERIOLOGIC FINDINGS

The identification of bacteria is not always a proof of pathogenicity, in both the pyogenic or zymogenic organisms, and yet often in what may be considered as normal organisms a pathogenicity due to them may exist, either because the strain had become perverted, or because of association with other bacteria. The following types may be considered as normal; coliform bacilli (*Escherichia coli*), aerobacter aerogenes, enterococcus, staphylococci, clostridia, bacteroides, and aciduric

bacilli (*Lactobacillus*, *acidophilus* and *bifidus*). Other organisms of pathogenic or zymogenic classification are found in disorders and apparently even in what has been designated as a normal intestinal tract. Among these are many and while they may exist without symptoms being present, nevertheless, because they often are found in gastro-intestinal complaints they should at times be viewed with suspicion rather than discounted as normal. In addition to the above and of more importance are the *proteus*, *pseudomonas* and *shigella*, the typhoid and paratyphoid bacilli, *alcaligenes fecalis*, *salmonella*, *enterobacteria*, *enterococci* (*strep* and *staph*), the anaerobes *clos. putrificus*, *welchii*, *oedematus*, *maligni*, and the *butyricum*, *tetani* and others not easy of identification. In the diarrheas of children the important organisms are *pseudomonas*, *proteus*, *paracolon*, *shigella*, *salmonella*, *streptococci*, *staphylococci*, *welchii*, *entericus B.* and *clos. putrificum* and these then are definitely in the pathogenic classification and should not be viewed as normal. Increasingly these organisms show evidences of clinical significance especially if present in predominant numbers, are persistent in the phagings, or when possible judged in suspicious associations.

For proper study all stool specimens should be collected under known condition of diet, especially important in the gross and chemical examination as compared with the bacteriological. They should be examined within 30 minutes of the defecation and immediately inoculated in ss agar, nutrient enriched broths and on Endo agar plates. Milzer, MacLean and McElwaine suggest as initial inoculations Selenite-F enriched broth, subcultured to bismuth-sulphate from triple sugar slants, from which single sugar inoculations are made. Sodium carbonate separation of streptococci is valuable as a side line observation for the streptococci species. The colonies are plucked and may be identified by various carbohydrate media, urea broth and re-inforced gelatin. Occasionally extra medias are necessary.

Of the greatest value in the bacterial examination of

feces is that which comes from the phaging procedures used by the author. In this a reinforced protein broth (2% dextrose bouillon) in two tubes is used. The purpose here is to pay less attention to the weaker types of bacteria that are phaged out early and to study the persistent types. The persistency added to that of predominance are two important items of etiological significance. The writer employs two tubes with the same media in each excepting one is boiled immediately before inoculation and quickly cooled. This is a so-called aero-anaerobic method, the media being covered with mineral oil or toluol. Each day for seven to fourteen days a specimen is taken from each of the two tubes, Gram stained and examined. In the average observation it will be observed that the mixtures of bacteria simplify and after a few days one or possibly up to three of the bacteria remaining. These may be taken out for culture identification and the therapeutic suggestions that may stem from this. Free sporulation in the anaerobic tube is always significant.

From these examinations clinical data of a valuable sort may be gained to explain the clinical findings in a case in both acute and chronic conditions. Commonly results from treatment are met by using bacteria from these phaging studies that are based on bacteriologic examinations that are most surprising in clinical ways. The latter is most often found in the organisms that belong to the pathogenic grouping *shigella*, *B. dysenteriae*, *paracolon*, *streptococci*, *pseudomonas*, *staphylococci*, *welchii*, *putrificus*, *butyricus* and *salmonella*.

The clinical conditions in which the biotoxic states as gleaned from proper stool examinations are many and important. Some of the states are direct and others contributory but often attention to the contributory is enough to bring about success from treatment. The applications of this work to medical conditions are too numerous to mention. It is difficult to understand how an internist or gastroenterologist can be successful enough in his work without these examinations being made and the suggested treatments carried out. In chronic disease this is especially important.

TUMORAL HYPERTROPHY OF THE GASTRIC MUCOSA: A CASE REPORT AND SUMMARY OF FINDINGS

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THE PURPOSE of this paper is to define and discuss the terms hypertrophic gastritis, gastric mucosal hypertrophy, and gastric polyposis. A case of tumoral hypertrophy of gastric mucosa is presented to be added to the sparse literature on this disease. Previous cases from the literature are reviewed especially considering the clinical and pathological features in an attempt to find any uniform or characteristic features. In reviewing the literature, cases of mucosal hypertrophy were found to be reported under many titles and not infrequently along with inflammatory or neoplastic disease. The choice of any single case in this review was made by comparing the pathological fea-

tures as presented in the literature to the "standard" features described below. Those thought not to be primary mucosal hypertrophy or whose descriptions were too inadequate are not included. Also it was found, as will be shown, that x-ray, gastroscopic, and clinical examinations are not in themselves sufficient at present for accurate diagnosis. Therefore, only cases with reported pathological descriptions are included in this review.

The terms hypertrophic gastritis and tumoral gastritis are not to be considered misnomers. These terms, however, are frequently misapplied to a condition of mucosal hypertrophy which we believe to be tumoral and not a reaction to inflammation or injury. Swelling of the mucosal folds with primary or essential in-

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inflammatory changes, as would be indicated by the term "hypertrophic gastritis," is a relatively common condition. However, enlargement of the folds with hyperplasia and insignificant or secondary inflammatory changes is infrequently reported and is a somewhat obscure and poorly defined condition (5, 19). Furthermore, since hypertrophic alterations of any kind in the mucosal patterns tend to be listed as "hypertrophic gastritis," it is not uncommon to find descriptions of polyps and polyposis included.

It is with the desire to aid in removing some of this confusion that the following descriptions of conditions usually included under the term "hypertrophic gastritis" are considered.

GASTRIC MUCOSAL HYPERTROPHY

(To be described in more detail later.) This term implies a pathologic change which is primarily mucosal overgrowth. Inflammatory changes may or may not be present. The concept of inflammatory origin based upon moderate inflammatory changes found in some cases assumes a lessened significance when it is considered how common such changes are in normal control adult stomach as noted by Heibel (14). The term also implies a hypertrophy of the mucosa due to hyperplasia of normal glands, but not due to adenomatous change.

This condition was best described by Menetrier (20) as polyadenomes en nappe and carefully distinguished

from adenomata by Heeks and Gibb (15), Pearl and Brunn (21), and by Eckhoff (11) and others. The stomach wall is thickened due essentially to mucosal hypertrophy. The mucosa forms large folds resembling cerebral convolutions. This alteration is diffuse involving the entire stomach, or involves large areas merging gradually into the normal mucosa. The mucosa forming the folds has a "cobble" or "pebbly" appearance. The essential microscopic feature is elongation of the glands with retention of the normal pattern and cellular differentiation (Fig. 2). However minor, and sometimes conspicuous, variations are noted. There may be areas of intestinalization (formation of colon-like cells), some glandular reduplication and formation of sinuous glands. Small cystic changes are common and appear to be obstructive. The muscularis mucosa remains intact, but may be stretched and penetrated by cystic structures in some instances. Such cystic changes are apt to occur about the bases of the tallest glands. The entire gland may be five to six times normal in height. The stroma may be somewhat thickened. Inflammatory changes, particularly those chronic in nature, are about as frequent as in average adult stomachs. When one considers the stagnation of stomach contents and secretions which must result from the deep folding of the mucosa resulting from hypertrophy, it would be surprising if more than usual inflammatory changes were not present.

GASTRIC MUCOSAL POLYPOSIS

This is a condition in which part or all of the stomach is covered by small grape-like masses. This was described by Menetrier (20) as polyadenomes polypeaux. Discrete polyps with independent attachments occur. They may be pedunculated or sessile and are usually soft. They are gray, ashy, brown or red in color and vary in size, but rarely are greater than 2 cms. in diameter. Their number varies from one to over three hundred (20) (2). Microscopically, the glandular epithelium is found on a sub-mucosal fibrous tissue core. The glands differ from normal in being elongated, tortuous, and dilated and composed of cells which are usually undifferentiated. Some glands may be "colonic" or perhaps contain Paneth cells (21); however, normal gastric cellular differentiation is not present. The hypertrophy in this instance is circumscribed.

HYPERTROPHIC GASTRITIS

This term implies an inflammatory origin of the observed changes. There can be little objection to using the term hypertrophic gastritis, if there is good evidence that such mucosal modifications were brought about by an inflammatory reaction. Defects in the mucosal architecture similar to those of mucosal hypertrophy described above can be brought about in the gross picture by cellular infiltration, edema, hyperemia, fibroplastic changes, etc.

This occurs in antral gastritis and is described in some detail by Crohn (10). This condition clinically resembles peptic ulcer without its periodicity and with a generally more severe course, but responding to ulcer management. In general, the mucosa is thickened and hyperplastic to the point of production of polypoid formations with defects varying from minute erosions to large discrete ulceration. Diffuse inflammatory

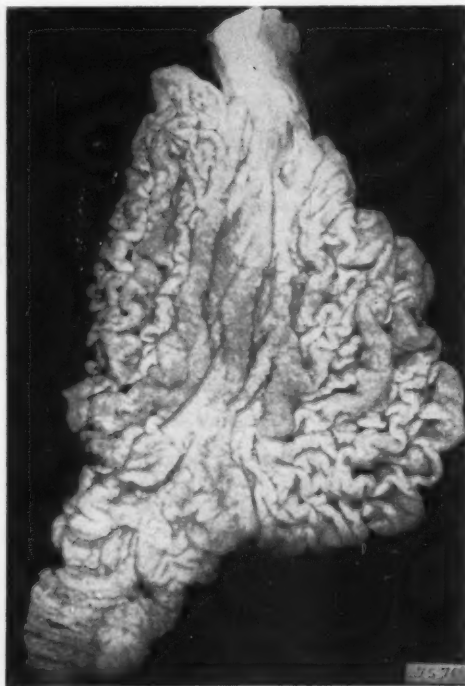
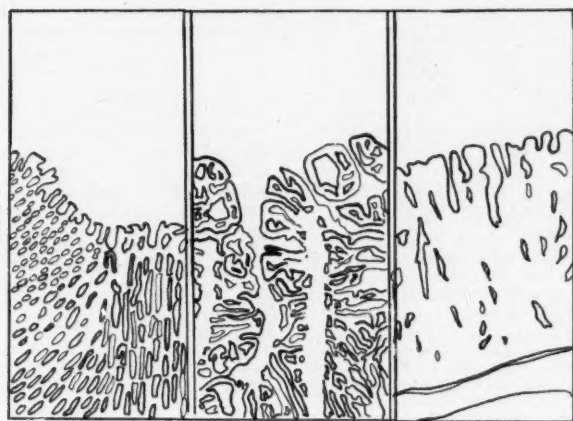


Figure 1.



A MUCOSAL HYPERTROPHY. Retention of normal glandular pattern.
 B MUCOSAL POLYPOSIS. "Adenomatous" mucosal pattern.
 C GASTRITIS. Separation of glands by inflammatory exudate.

Figure 2.

changes are present. The muscularis mucosa is markedly hypertrophied. The submucosa is often thickened as in linitis plastica. The case of hypertrophic gastritis reported by Eckhoff (11) fits this category best. Spriggs (24) reports a number of cases of mucosal hypertrophy caused by gastritis, many of which followed gastrojejunostomy.

The changes are definitely not neoplastic and the mucosa may return to normal or regress to atrophy. The lesions are not circumscribed or demarcated from the neighboring tissue, nor are the glandular irregularities of adenoma found. Cellular metaplasia may occur.

CASE HISTORY

A fifty year old white lawyer was admitted in April, 1949, with symptoms of renal failure. There was a history of acute nephritis thirteen years previously with full clinical recovery, but a return of similar symptoms in November, 1948. His chief complaints on admission were headache, slight dyspnea, ankle edema, nocturia and frequency of urination. There was no history of gastro-intestinal distress of any kind up to two weeks prior to admission in November when he began to complain of a bitter taste and non-periodic nausea without vomiting. He did not appear acutely ill. His heart was enlarged and his blood pressure was 254/160 mm. Hg. Examination of the abdomen was negative.

Urinalyses showed a persistent albuminuria, low fixed specific gravity, and granular casts and rbc's. There were 12 gm. of Hb., 5.0 million rbc's and 9.0 thousand wbc's. The stools were negative for blood on repeated examinations. The gastric secretions were described as turbid and mucilaginous. The free HCl rose to 47 degrees 4 minutes after histamine.

X-rays of stomach after a barium meal revealed coarse folds throughout the entire body and prepyloric antrum. The folds seemed over 16 mm. across. The diagnosis was giant tumoral gastritis. Gastroscopic examination revealed "large gastric folds."

A single rectal polyp was removed and showed dark adenomatous crypts, nuclear crowding and numerous mitotic figures, but was not considered malignant.

He was discharged after three weeks in an improved condition. Thiocyanates and digitalis were given. He returned on

May 18, 1949, in renal failure and expired on May 26, 1949.

At autopsy there were no evidences of malnourishment. Edema was minimal. There was mild ascites. The heart weighed 680 grams. The kidney showed combined evidences of severe arteriolar nephrosclerosis and old pyelonephritis. There was severe generalized atherosclerosis and passive congestion of all organs.

The serosal surface of the stomach was normal. There were no enlarged lymphnodes in ligamentous attachments. The enlarged rugae were easily palpable through the wall. The mucosal surface is illustrated (Fig. 1), showing enlarged mucosal folds extending throughout entire stomach from esophageal-cardiac junction to pylorus.

Microscopically, the mucosal glands are hypertrophied and average about 3.5 mm. in length, but vary from about 2 to 5 mm. Cellular differentiation is normal (Fig. 2). Inflammatory cellular reaction within the stroma is generally absent, but may be found in some areas, as in any average adult stomach. In many areas, but especially at the base of very elongated glands, there are cystic changes, apparently obstructive in nature. These are seen occasionally to traverse the thinned muscularis mucosa (as seen by Maimon et al (19)). The latter is seen to take part in the formation of the enlarged mucosal folds and may be seen in some places to be moderately hypertrophied. The submucosa and muscularis are not remarkable.

The following is an analysis of 26 cases from the literature. Each case is believed to be tumoral hypertrophy of the gastric mucosa. Cases selected are indicated in bibliography.

CLINICAL FINDINGS

The ages were stated in 24 of the cases. The range was from 26 to 72. However, 20 of the 24 (20/24) ranged from 32 to 59, the average being 44. The other 4 cases were 26, 71, 71, and 72 years of age.

The sex was stated in 23 instances and there were 16 males (16/23) and 7 females (7/23). The race usually was not stated, but one case occurred in a colored female.

Three cases (3/23) were reported to have had no gastro-intestinal symptoms. In two cases the duration of symptoms was "years," and in 4 cases over 9 years. In the bulk of the cases the history was of comparatively short duration, three years and less in 12 (12/23) cases, and less than a year in 9 cases.

Mid-epigastric pain or discomfort was the most common symptom, being present in 13 out of 19 patients (13/19), lower abdominal pain was recorded in 3/19, and right upper

quadrant pain in 2/19. This was described as fullness, pressure, or gas in 8/19, burning or gnawing in 5/19, as "pain" in 3/19, and cramping in 2/18. It was relieved by food or alkalis in 9/14 of the cases, not relieved by diet or alkalis in 2/12, and made worse by food in 2/12. The relationship to meals was stated 6 times and in 5/6 it occurred from one half to several hours after meals.

Nausea and vomiting were recorded in eleven cases and in two cases the vomitus was blood streaked and in one case it was termed hematemesis.

Weight loss was found in 16 cases. This varied from about a pound a month loss in cases in which the symptoms were of 12 to 36 months duration to about 5 pounds a week in cases with severe acute gastric upsets.

Statement of physical findings was recorded in 16 cases and of these abdominal tenderness was found in 8 instances; no other pertinent physical signs were recognized.

Gastric analyses were done in 20 cases. No free acid was found in 7/20, but in 4 of these the total acid ranged from 7 to 22 degrees. The free acid ranged from 10 to 49 in 8/20, and was 90 to 130 in 2/20. In two other cases (2/20) acid was "present" and in an additional case (1/20) the acid was "low." Blood was found in stomach contents of three cases.

The stools were positive for occult blood in four cases. There were but two cases of distinct anemia.

ASSOCIATED DISEASES

There were two cases in which similar hypertrophic changes occurred in other parts of the body. In one case (13) there was hypertrophy of mucosa of small bowel and of the bladder and ureters. In another case (23) there was hypertrophic involvement of all of small bowel and part of large bowel. One case was associated with carcinoma of stomach (8).

There were also two cases of peptic ulcer (duodenal and gastric), one case of nonspecific ulcerative colitis, one case of chronic constipation, one case of obstructive biliary disease, one of hypopituitarism and one case of pyelonephritis.

Of these associated diseases it would seem that the first mentioned might be of significance in determining an "essential" etiology.

GASTROSCOPY

Examinations were made in 13 cases. In five (5/13) carcinoma was diagnosed. This does not include the case of proved carcinoma (8) noted above, in which the gastroscopic diagnosis was tumor simulating gastritis, or "extrinsic gastric tumor." Hypertrophic folds were noted in 3/13, and other diagnoses, namely: suspected intramural tumor, benign gastric tumor, tumor simulating gastritis, polyposis and "precancerous lesion" were made. One report (23) presented a case of hypertrophic gastritis (conforming to tumoral hypertrophy) wherein a gastroscopic diagnosis of carcinoma was made. An operation was undertaken, but the patient died postoperatively.

X-RAY

Examinations were made in 25 cases. Of these carcinoma was diagnosed in thirteen instances (13/25), including the single case (8) in which carcinoma was found on pathology examination. Polyps were diagnosed in 6/25, tumor mass in 3/25, and "lobulated mass," large soft folds, and inconstant filling defect in the remaining cases.

Subtotal gastrectomy was performed in 10 cases and

a total gastrectomy in three. Pathologic examinations were made in other cases by biopsy and autopsy.

PATHOLOGY—GROSS ASPECTS

The location of the lesion was indicated in 14 cases. It was found in upper portion of the stomach in 4 instances (4/14), involved the whole stomach in 5/14, the greater curvature in 2/14, and in the pylorus and antrum in 3/14. The size of the involved areas, in cases in which whole stomach was not involved, was noted in 4 instances, 8x7 cms., 10x19 cms., 8x7 cms., and 17x18 cms.

The appearance of the mucosal surface was not usually described, but was stated to have been pebbly or cobbled in 6 cases. The color was mentioned only 4 times, 3 times as purple or violaceous and once as pink.

The rugae were said to be greatly enlarged or "cerebriform" in all instances, but measurements were found only in 7 cases. The widths varied from 0.5 to 2.5 cms. and heights from 0.8 to 3 cms. The rugae were described as "polypoid" in two cases, and as irregular in two cases.

Lesions of the mucosa were noted in 8 cases. Small erosions or ulcers were found in 6 and two of these were associated with punctate hemorrhages. Edema and inflammation were found in one case, small areas of gastritis in one, and chronic ulcers in two cases as noted above.

The margins of the hypertrophied tissue are never circumscribed, but fade gradually into the surrounding mucosa. Occasionally, tiny cysts can be seen in the mucosa. The wall is generally described as thickened, but not stiff or indurated as the case of carcinoma or primary inflammation or ulcer. The serosa is usually described as normal, although unusual prominence of the blood vessels was noted in 3 cases. Enlargement of lymphnodes was noted once along the mesentery of the lesser curvature and once along both curvatures.

MICROSCOPIC FEATURES

The gastric glands are usually described as elongated, but sometimes they are merely stated to be "hypertrophic" or "hyperplastic." However, in practically every case the configuration is stated to be normal with some variations. In nine cases cystic changes are noted. In 6 cases focal corkscrew formations or tortuosities are present. Distended glands are seen in two. The cystic changes are most apt to occur at bases of longest glands. Focal glandular penetration through the muscular mucosa is described in 5 cases.

In general, the cells show normal differentiation. However, focal "intestinalization" is seen in 2 cases. Cellular crowding and focal pleomorphic changes are remarked upon in two instances.

Descriptions of stromal exudative changes are most difficult to interpret, largely because the extent of such changes constituting definite disease is at present unknown. However, dense infiltration of the stroma with plasma cells or lymphocytes is noted in 4 cases. In 4 other cases edema, edema and "chronic inflammation," and edema and "congestion" were seen. In another case a slight increase in connective tissue was thought to have contributed to the rugal deformity. The muscularis mucosa was described as thickened in 2 cases.

In five cases fibrosis of the submucosa is described. Other changes are seen in single instances: edema and increased vascularity, edema in large folds, dilatation of lymph channels, and "thickening" edema.

These connective tissue changes cannot be considered as typical of the series or essential to the disease.

DISCUSSION

It is seen, then, that the average case is more apt to occur in a male, especially in the 4th, 5th, or 6th decade of life. The history of gastro-intestinal disturbance is likely to be of less than three years duration, and to consist of mid-epigastric pain or discomfort which may or may not be relieved by ingestion of food or alkali. This discomfort probably will show little periodicity. Nausea and vomiting or weight loss might be the presenting complaint. Abdominal tenderness is as likely as not to be absent. Palpation of tumor would not be expected.

Gastric analysis will generally reveal a low acidity. The presence of blood in gastric content or stools is unusual, but will parallel the severity of symptoms. Anemia is not a common concomitant finding.

X-ray and gastroscopic examinations are very likely to be misleading, but the latter is considerably more reliable.

It is readily seen that the clinical syndrome is still not sufficiently distinctive to allow a diagnosis, but this condition is deserving of consideration when this train of findings is discovered.

This is especially so since the frequency and importance of this condition is, at present, almost completely unknown. It is rarely reported, but yet fairly large series are reported in some detail by some institutions, for example Maimon et al (1). The finding of "hypertrophic gastritis," which as we have noted may be one of several conditions, has been found to be of varying incidence in large gastroscopic and x-ray clinics, from .008% to .43% (1). Some fairly large series, most likely representing gastric mucosal hypertrophy, but lacking definite pathologic substantiation have been published. An example is the report of cases 54 to 65 of Spriggs (24). These 12 cases are of "gastric swelling without known ulcer or trauma" and are very similar, in general, to the case reviewed by us. There were 9 men and 3 women with average age of 52. The sites of involvement were cardia 7, midstomach 2, and general involvement 3. Epigastric pain and discomfort occurred in 7, eructation in 5, nausea in 5, vomiting, weakness, and headache in 4, anorexia and wasting in 3, diarrhea in 3, and constipation in 3. Anemia was severe in 2 and moderate in 3 patients. Hydrochloric acid was absent in 6, almost absent in 1, low in 3 and normal in 3. Spriggs considered the condition as reversible and this seemed to be so in one case.

It seems very likely that gastric mucosal hypertrophy has generally been overlooked.

Certain statements found in the literature have not been able to confirm. It is stated that "polyadenome en nappe" is quite common (12). This may be so, but well documented cases are rarely reported. It is stated that it is very prone to malignant change (12, 16), but

it seems more likely that the diagnosis was not definitely established in the first place as a prior condition. We have seen grossly; typical "hypertrophic gastritis" closely simulating "polyadenome en nappe" or gastric mucosal hypertrophy, which was carcinoma microscopically.

SUMMARY

We have presented one case of hypertrophy of the gastric mucosa which seemed "primary" in nature. We have reviewed an additional 25 cases in an attempt to separate this condition from others with which it is often confused.

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POST-NECROTIC (TOXIC) CIRRHOSIS: ITS CLINICAL SIGNIFICANCE

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INTRODUCTION

IN 1911, Mallory (1) delineated toxic cirrhosis as a morphologically distinctive type of cirrhosis that follows relatively acute and extensive necrosis of the liver cells. Twenty-one years later, he presented his findings in 550 cases of cirrhosis, of which 46 were of this type (healed acute yellow atrophy) (2). Pratt and Stengel (3) reemphasized the specificity of this lesion and presented the clinical aspects of five such cases. A wide variety of confusing classifications of cirrhosis, based on morphological, etiological and clinical characteristics, have been presented in the medical literature; Karsner (4) in 1943, tried to bring some order from this chaos in his division of cirrhosis into ten fairly characteristic groups, preferring the term post-necrotic cirrhosis to either of the designations that Mallory had used. In spite of the frequent autopsy demonstration of transitional stages between post-necrotic and Laennec's cirrhosis, and many differences in descriptive nomenclature, this group of chronic liver diseases retains today a specific identity, at least morphologically, in most pathology laboratories. The question arises as to whether any such distinction can be made on clinical grounds.

The symptomatology varied widely in the five cases presented by Pratt and Stengel. In their exhaustive analysis of the clinical aspects of 386 cases of *Laennec's cirrhosis*, Ratnoff and Patek (5) included four presumptive cases of *toxic cirrhosis* without attention to possible differences from the remainder of their cases. Kunkel and Labby (6) reported five patients in whom cirrhosis followed infectious hepatitis; the cirrhosis being of the post-necrotic type, morphologically, and differing in its clinical course from that usually seen in *Laennec's cirrhosis* in being progressive and unresponsive to treatment. In the last few years, following Lucke's more optimistic report (7) in 1944, there has been a growing body of reports (8-14) emphasizing the possibility of *chronic liver damage* following infectious hepatitis. It seems likely that this type of cirrhosis will be a more common pathological and clinical finding in the future than it has been so far.

METHOD AND FINDINGS

In the present study, 6,184 autopsy records for the 19 year period, 1931-1949 inclusive, at Michael Reese Hospital, were reviewed, disclosing 10 cases that conformed morphologically to the post-necrotic (toxic) type of cirrhosis, among 95 cases of cirrhosis of all types. The incidence of post-necrotic cirrhosis in this series is then 0.17% of the autopsied cases. The criteria for this diagnosis as indicated by Karsner were (a) grossly, a diffusely scarred liver, showing irregular bands of dense connective tissue both coarse and fine,

and lacking the uniformity of nodulation of *Laennec's cirrhosis*; and (b) microscopically, marked distortion of the architecture, and in many fields broad masses of connective tissue with little or no parenchyma left, often marked proliferation of bile ducts and nodules of proliferated hepatic cells.

The clinical records of these ten cases were reviewed for the purpose of comparing the course of this type of cirrhosis with that of *Laennec's cirrhosis*. The series of Ratnoff and Patek was chosen as the basis of comparison.

Age and sex distribution of the patients is indicated in Table I. No particular conclusion seems justifiable, except that this condition may occur at almost any age, and in either sex, although it is somewhat more frequent in males.

Particular attention was paid to possible etiological factors in the past history of these patients, and these, where found, are also shown in Table I. In none of these cases was there evidence antecedent infectious hepatitis had occurred. However, in the fifteen month old child (Case X), there was a history of the child's father having had infectious hepatitis in the military service prior to her birth; and after her death, a sibling developed severe jaundice. Other possible predisposing conditions were divided into antecedent disease, concurrent disease, and exposure to hepatotoxins. In the first category, relevant past illnesses were typhoid fever in two cases, severe hyperthyroidism in one, and infantile diarrhea in the child. Four patients had concurrent disease that might have been related to liver damage: hyperthyroidism in Case II, arthritis in Case III, undulant fever in Case IV and carcinoma of the pancreas, diabetes mellitus and cholelithiasis in Case VII. One patient had been treated with sulfadiazine, and one with cinchophen, while three of the patients used alcohol excessively.

TABLE I

Case Number	Age	Sex	Exposure to Hepato- toxins or Infections
I	61	M	Alcohol, typhoid fever
II	40	M	Alcohol, hyperthyroidism
III	59	M	Cinchophen, arthritis, typhoid fever
IV	54	M	Hyperthyroidism, undulant fever
V	26	F	Alcohol
VI	56	M	—
VII	68	F	Diabetes, cholelithiasis
VIII	53	M	Sulfadiazine
IX	65	F	—
X	15 mo.	F	Infantile diarrhea, (possible infectious hepatitis)

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The symptoms and signs are listed in Table II. Jaundice, edema and ascites were classed as symptoms when the complaints of the patient suggested their presence; they were classed as signs when included in the description of the physical examination. Since in each case, when present, they were listed under both categories, for the sake of simplicity this distinction is not made in the table. Case VI was that of a man with severe lobar pneumonia who died after two days in the hospital, in whom toxic cirrhosis was an incidental autopsy findings, of which he presented neither symptoms nor signs. Case VII was that of a woman who at autopsy presented a typical picture of toxic cirrhosis, which was felt to be independent of the carcinoma of the pancreas which was the source of her clinical manifestations. In considering the incidence of signs and symptoms, therefore, these two cases are disregarded.

TABLE II
SYMPTOMS AND SIGNS IN POST-NECROTIC CIRRHOSIS

Case Number	Jaundice	Hepatomegaly	Edema	Ascites	Right upper quadrant pain	Weakness	Splenomegaly	Weight loss	Stupor	Nausea	Comment
I	x	x	x	x	x	x	x				Diarrhea
II	x	x			x	x			x		Enlarged thyroid, tremor
III	x		x	x					x		
IV	x		x				x				Telangiectases
V	x	x					x			x	
VI											Related only to lobar pneumonia
VII											Carcinoma of pancreas
VIII		x									"Indigestion"
IX	x	x			x		x				Right pleural effusion
X	x	x	x								
Total	5	5	5	3	2	3	2	2	2	2	1

(Excludes
VI & VII)

With respect to laboratory data, very little information is available in these cases, since, for the most part, the patients died in the years prior to the easy availability of extensive laboratory studies related to liver function. In four instances the van den Bergh reaction was tested, and uniformly showed immediate positive reaction both direct and indirect. Five of the cases had determinations of total cholesterol and percentage of esters, and in each instance the total figure was within normal limits, while the esters were reduced to 46%, 42%, 27%, 21% and 8%. In three cases the ratio of albumin to globulin in the serum was 2.9/3.4, 2.3/4.1 and 3.3/2.9.

Prior to death, symptoms were present in eight of these patients for two months to eight years, with an average duration of twenty-seven months. The immediate cause of death and duration of symptoms prior to death in each case is indicated in disclosed a markedly icteric man with pulse of 120 and blood

Table III. It may be seen that, excluding the patient with carcinoma of the pancreas, four of the patients died in cholemia or hepatic failure. Three patients had gastro-intestinal hemorrhages, two from esophageal varices and one from an acute duodenal ulceration. (At autopsy, Cases V and IX also had demonstrable varices of the esophageal veins, but without hemorrhage). The remainder of the group died of inter-current, acute pulmonary disease.

TABLE III

Case Number	Duration of Symptoms	Cause of Death
I	21 months	Pneumonia, circulatory collapse
II	25 months	Cholemia
III	10 months	Cholemia, bleeding varices
IV	12 months	Cholemia, acute duodenal ulcer with hemorrhage
V	48 months	Cholemia
VI	no symptoms	Lobar pneumonia
VII	(3 months)	(Cholemia), Carcinoma of pancreas
VIII	no symptoms	Circulatory collapse, bleeding varices
IX	8 years	Pneumonia, incarcerated femoral hernia with infarct of bowel
X	1 year	Malnutrition, hemorrhagic infarct of lungs

CASE SUMMARIES

Case I. A 61 year old white male was admitted to the hospital on December 31, 1932, having had constant burning pain in the right upper quadrant of the abdomen and progressive weakness for twenty months, recurrent diarrhea for one year, and evidence of ascites and edema for the previous two weeks. He had had typhoid fever forty years before and had been drinking a quart of wine daily for at least four years. On examination there was no jaundice; the abdomen was markedly distended with ascitic fluid, and the legs were edematous. Following paracenteses of nine, ten and eleven liters of fluid, at about two week intervals, the liver was palpable two to three centimeters below the costal margin and the spleen was palpable one centimeter below the costal margin.

After one month in the hospital, he developed a fever to 101°F., rales at both lung bases, and dyspnea. Following the last paracentesis his blood pressure fell to 68/50, his pulse became rapid and weak, and after a few hours, he expired.

MAIN AUTOPSY FINDINGS: 1. Cirrhosis of the liver (toxic). 2. More recent thrombosis of portal and splenic veins. 3. Ascites. 4. Fibrosis of the spleen—splenomegaly. 5. Bilateral broncho-pneumonia.

CASE II. A 40-year-old white male, admitted to the hospital on May 19, 1933, with complaints of nervousness and progressive weakness and right upper quadrant abdominal pain for the previous six months. Jaundice had developed one week prior to admission. In May of 1931 and again five months later, this patient had been studied in the hospital with typical symptoms and findings of hyperthyroidism, for which he had refused operative treatment. He had taken excessive amounts of alcohol over many years. Physical examination

pressure of 130/74, tremor of tongue and hands, palpable thyroid isthmus, a tense tympanic abdomen with the slightly tender, irregular liver edge palpable two centimeters below the umbilicus. The erythrocyte count was 2.15 million and hemoglobin 50%, the urine showed a trace of albumin, a normal sediment, and two plus bile; the stool was negative for occult blood; icterus index was 82 and the van den Bergh reaction was positive—direct and indirect.

The jaundice progressed; the patient became irrational and had to be restrained, and two weeks after admission to the hospital he died.

MAIN AUTOPSY FINDINGS: 1. Toxic cirrhosis of the liver. 2. Severe icterus. 3. Ascites (1000 c.c.). 4. Chronic gastritis and duodenitis. 5. Subacute splenic hyperplasia. 6. Cloudy swelling of the kidneys. 7. Chronic passive hyperemia of the lungs.

CASE III. A 59-year-old white male was admitted to the hospital on February 2, 1938, in a semi-stuporous condition. The history was obtained that about one year previous, he had had some type of acute arthritis for which cinchophen (total dose 12 Grams) was prescribed. About two months thereafter he developed jaundice which lasted several weeks and subsided slowly; no ascites was present. He was well until five weeks prior to admission when pain and swelling appeared in the left wrist. Again, on the advice of his physician, he took cinchophen in a total amount of 4 Grams. Three weeks later abdominal enlargement and edema of the legs appeared, and after another week jaundice was evident. The jaundice progressed and he became drowsy and then semi-stuporous. He had had typhoid fever. The total cholesterol in the serum was 147 mgm% of which 21% was esterified; icterus index was 54 and the van den Bergh gave strong immediate reactions both on the direct and indirect test; the albumin/globulin ratio was 2.9/3.4.

On the second hospital day, 5,500 c.c. of clear fluid was removed from the abdomen by paracentesis. On the third day, the patient became comatose and suddenly developed a massive hematemesis, part of which was aspirated. This was followed by cyanosis and death.

MAIN AUTOPSY FINDINGS: 1. Toxic cirrhosis of the liver. 2. Esophageal varices with hemorrhage into the stomach. 3. Aspiration of blood into the trachea and bronchi. 4. Jaundice. 5. Ascites (3000 c.c.). 6. Edema of the lower extremities, intestines, and diaphragm. 7. Bilateral hydrothorax (100 c.c.). 8. Early fibrosis of the spleen.

CASE IV. This patient, a 54-year-old white male, was first hospitalized from July 3, 1937, to September 24, 1937, for a subacute febrile illness during which a positive blood culture was obtained for *Brucella abortus* and blood agglutination tests for *B. abortus* were consistently positive in titres rising from 1:160 to 1:2560. He had had a hemithyroidectomy in 1929 for severe thyrotoxicosis and x-ray therapy for recurrent hyperthyroidism in 1933. In 1937, during this febrile illness he had a marked tremor of his hands, head and feet, moderate exophthalmos, pulse rate of 120-130, blood pressure 150/80, mild enlargement of the liver, and basal metabolic rate of plus 47%. Following his discharge from the hospital he was taking Lugol's solution and got along fairly well, gaining five pounds. In February of 1938 he developed diarrhea without pain, nausea, or vomiting and one week later was observed to be jaundiced. He was readmitted to the hospital on March 28, 1938, being deeply jaundiced and showing many telangiectases and pitting edema of the legs and sural area. The liver and spleen were not palpable. His icterus index was 106; the albumin/globulin ratio was 2.3/4.1 and the cholesterol was 113 and 107 with esters of 8% falling to 0. His course was progressively downhill and one week after admission he died in cholemia.

MAIN AUTOPSY FINDINGS: 1. Toxic cirrhosis of the liver. 2. Severe icterus. 3. Acute duodenal ulcer with hemorrhage (150 c.c. blood in stomach). 4. Subacute splenic hyperplasia. 5. Acute glomerulonephritis (beginning). 6. Ascites.

CASE V. This 26 year old female was admitted to the hospital on December 1, 1936, having noticed jaundice and dark urine throughout the preceding year. For more than a year prior to the onset of jaundice, she had been drinking large amounts of wine, beer and whiskey. She had had no itch-

ing, chills, pain or light colored stools. Four weeks before admission, she had an acute upper respiratory infection with pain and swelling of the right knee. She was deeply icteric, had a large, hard spleen and enlargement of both lobes of the liver. A mass was palpated in the epigastrium. However, at exploratory laparotomy on January 29, 1937, the only abnormal findings were a large nodular liver (microscopically diagnosed as toxic cirrhosis) and a firm, moderately enlarged spleen. She was discharged on February 18, 1937. On July 28, 1939, she was readmitted, having been jaundiced continuously since her previous admission. She was now comatose and bleeding from her mouth; had marked clubbing of fingers, edema of legs, large liver and spleen, but no evidence of ascites. Her condition deteriorated and on August 3, 1939, she died. During her course the icterus index fluctuated widely, from 22 to 141, but was usually over 70; the total cholesterol was consistently between 133 and 154 mgm% with 31 to 43% esters, the van den Bergh gave strong immediate positive reactions, both direct and indirect and the albumin/globulin ratio was 3.0/4.1.

MAIN AUTOPSY FINDINGS: 1. Toxic cirrhosis of the liver. 2. Icterus. 3. Splenomegaly (fibrosis, hyperplasia and passive hyperemia). 4. Icterus nephrosis. 5. Chronic gastritis and enteritis. 6. Esophageal varices. 7. Chronic hyperplasia of portal and peri-cholestatic lymph nodes. 8. Dilatation of common bile duct (no stones). 9. Hydrops of gall bladder, chronic cholecystitis. 10. Chronic salpingitis and bilateral hemosalpinx.

CASE VI. A 56-year-old white male was admitted to the hospital on January 24, 1942, and died two days later. He was semi-comatose and irrational; however, the history was obtained that he had not been known to have serious illness previously. The physical findings were those of consolidation in the right lung. No laboratory data were available.

MAIN AUTOPSY FINDINGS: 1. Lobar pneumonia, right upper and lower lobes. 2. Acute fibrinopurulent pleuritis. 3. Acute anterior mediastinitis. 4. Acute splenic hyperplasia. 5. Early toxic cirrhosis of the liver (incidental). 6. Moderate generalized arteriosclerosis.

CASE VII. A 68-year-old white female was admitted to the hospital on March 17, 1944, complaining of right upper quadrant abdominal pain and jaundice of two months' duration and a weight loss of 15 pounds in six months. Stones had been demonstrated in her gall bladder and a diagnosis of diabetes mellitus made eight years previously. She was markedly jaundiced and had an enlarged, tender liver, palpable four centimeters below the xiphoid and a palpable gall bladder. The van den Bergh was immediately positive direct and indirect; the cholesterol was 230 mgm% with 27% esters. The symptoms progressed and the patient became stuporous and finally developed fever and rales in both lungs and died on April 6, 1944.

MAIN AUTOPSY FINDINGS: 1. Carcinoma simplex of the head of the pancreas with metastases to the regional lymph nodes. 2. Extension to the second portion of the duodenum with ulceration. 3. Compression of the bile ducts. 4. Jaundice. 5. Chronic cholecystitis and cholelithiasis. 6. Toxic cirrhosis of the liver. 7. Splenomegaly. 8. Ascites. "The liver presented an advanced cirrhosis of the toxic or post-necrotic type, with superimposed more recent changes. The cirrhosis of the liver in this instance must be considered as a completely independent lesion, not correlated in any way with the carcinoma of the pancreas."

CASE VIII. On October 4, 1946, this 53-year-old white male was admitted to the hospital following a sudden onset of dyspnea, orthopnea, weakness and cough productive of pink sputum. Slight edema of the ankles was present for about three weeks. In his past, the only serious illness had occurred one and one-half years before, at which time he was hospitalized with a syndrome suggestive of acute appendicitis. Following the removal of a grossly normal appendix, his serial electrocardiograms were suggestive of an atypical myocardial infarction. He was kept in bed for six weeks, treated with sulfadiazine for one week post-operatively, as well as with digitalis, aminophyllin and papaverine. Following this he was quite well until the present admission. His blood pressure on admission was 200/88, pulse 136 with frequent extra-systoles; there was flatness to percussion over the entire right chest, enlargement of the heart with an apical systolic murmur, dis-

tention of the abdomen and moderate edema of the legs. The liver and spleen were not palpated. On the morning of the second hospital day, 1300 c.c. of clear fluid was removed from the right pleural cavity with marked symptomatic improvement. However, that evening the blood pressure fell to 70/40, the patient became cyanotic and dyspneic and died.

MAIN AUTOPSY FINDINGS: 1. Cirrhosis of the liver, post-infectious. 2. Dilatation of esophageal and gastric veins. 3. Massive gastro-intestinal hemorrhage (1000 c.c.). 4. Early bronchopneumonia. 5. Mild ascites. 6. Right hydrothorax. 7. Nephrosclerosis and calcium casts of renal tubules. 8. Splenomegaly.

CASE IX. A 65-year-old white female was admitted to the hospital on June 2, 1946, acutely ill, weak and emaciated. She had first been seen in the hospital in October 1945 with complaints of ankle edema, fatigue and exertional dyspnea for six years, increasing in severity during the preceding four months and associated with anorexia, weight loss of 17 pounds and aching lower abdominal pain. The past history was negative with the exception that she had had three abdominal operations many years before for vaginal bleeding, the exact pathology not being known. The sclerae appeared slightly icteric, the lower half of the right chest was dull to percussion, the heart was enlarged and a systolic murmur was heard at the apex; the liver was palpated four and one-half centimeters below the costal margin and was hard and slightly tender; the legs were moderately edematous. The icterus index was 12. The bromsulphalein test showed 45% retention at 75 minutes, the albumin/globulin ratio was 3.3/2.9 and the van den Bergh showed immediate faint positive direct and immediate moderately positive indirect response. She had several thoracenteses and was discharged. In March 1946 she was again hospitalized because of increasing dyspnea and the same findings were observed. She had two more thoracenteses, each yielding six quarts of cloudy fluid. At the time of her last admission in June 1946, she again had a massive right pleural effusion, marked peripheral edema and hepatomegaly. She became comatose and died twenty-four hours after admission.

MAIN AUTOPSY FINDINGS: 1. Toxic cirrhosis of the liver. 2. Esophageal varices. 3. Ascites. 4. Right hydrothorax and partial collapse of the right lung with bronchopneumonia. 5. Acute fibrinous pleuritis (right). 6. Incarcerated right femoral hernia with hemorrhagic infarct of incarcerated loop of ileum. 7. Chronic peptic ulcer of stomach. 8. Generalized arteriosclerosis. 9. Edema of lower extremities.

CASE X. This female child was born by normal delivery at full term on November 25, 1946, with a birth weight of 6 pounds and 2 ounces. She was well for three weeks and then her abdomen became distended and she passed excessive flatus. After another week diarrhea began and responded only briefly to change in formula. At the time of her first admission to the hospital on January 25, 1947, she had been jaundiced for two weeks and was having six loose, whitish-yellow stools per day. Both parents were at that time in good health although the father gave the history of having had acute hepatitis in the tropics in 1944. (Subsequent to the death of this patient, a sibling developed acute hepatitis). On examination the child was jaundiced but well-nourished and not acutely ill; the superficial veins over the abdomen were prominent and the abdomen distended; an umbilical hernia two centimeters in diameter was present and the liver was enlarged, the edge being palpable three and one-half centimeters below the costal margin. Bile was found in the urine but not in the stool; the total cholesterol was 156 mgm% with 42% esters. Stools were negative for amoebae and pathogenic bacteria. On February 7, an operation was performed. A small amount of slightly bile-stained material was found in the gall bladder, which was drained. No common or hepatic ducts could be found and these were presumed to be absent. The post-operative course was complicated by fever, diarrhea and eversion. The patient failed to gain weight and jaundice increased. The serum bilirubin reached 7.6 mgm. She was discharged on March 28, 1947. Out of the hospital, the child improved and got along quite well for nine months when, following an upper respiratory infection, the abdomen became swollen. She was readmitted on January 21, 1948, with findings very much as on the previous admission, with

the exception that there was no jaundice. Serum cholesterol was 240 mgm% with 60% esters and the stools were positive for bile and urobilinogen. On February 8, diarrhea and vomiting began, followed by marked dehydration. Proteus morgani was isolated from the stools. Fever and difficulty in respiration occurred and she died on February 16, 1948, at the age of fifteen months.

MAIN AUTOPSY FINDINGS: 1. Toxic cirrhosis of the liver. 2. Patent cystic, common, and hepatic ducts. 3. Fibroadenoma of the spleen. 4. Ascites, marked; bilateral hydrothorax, and minimal hydropericardium. 5. Marked dilatation of superficial veins of chest and abdomen. 6. Hemorrhagic infarction of lung, small. 7. Umbilical hernia. 8. Hemorrhages of lung and pericardium.

COMPARISON WITH LAENNEC'S CIRRHOSIS

While the number of cases presented here is small for statistical correlation with the series of Ratnoff and Patek, it is felt that this group of cases is sufficiently large to detect any marked differences in trend of the clinical antecedents and course of this condition from the figures presented for Laennec's cirrhosis. Although a wide distribution of ages is found here, indicating that toxic cirrhosis may occur at any age, seven of the ten cases fell into the period from age 40 to 65, in which Laennec's cirrhosis has its maximum incidence. Males predominate in our series in the ratio 6:4, whereas in Laennec's cirrhosis, the male preponderance is even greater. Only three of our ten patients were alcoholics while 54% of the cases in Ratnoff and Patek's series fell in this category. No case of syphilis was present in our series in contrast to 16% in their report. Our failure to find any case with a history suggestive of antecedent infectious hepatitis is consistent with the low incidence (6.5%) of history of previous episodes of jaundice in the Laennec's cirrhosis series. In only one of our cases did exposure to a chemical toxin seem to play a convincing part, namely, the patient who was treated with cinchophen. The presence of two cases with thyrotoxicosis in this series of ten would seem to be significant (15-17).

The initial symptom in our cases was jaundice in three, edema of the lower extremities in two, and in one case each, weight loss, weakness, and abdominal pain. In the other two cases, lobar pneumonia and carcinoma of the head of the pancreas were responsible for the predominant symptoms. This differs sharply from the presenting symptom in Ratnoff and Patek's study, in which the following order of frequency pertained: swollen abdomen (27.7%), abdominal pain (12.4%), hematemesis (10.1%), edema of the lower extremities (9.6%), and jaundice (8.8%). In general, the incidence of gastro-intestinal symptoms such as weight loss, anorexia, nausea, vomiting and swollen abdomen seem relatively less frequent in our cases than in the Laennec's cirrhosis series.

The principal clinical signs of post-necrotic cirrhosis seem to differ very little from those of the Laennec type, with one exception. Whereas ascites was the most common finding in the latter group, being detectable in 78% of the cases, in the ten cases that we studied, only three had sufficient ascitic fluid to be detectable on physical examination. On the other hand, at autopsy, some degree of ascites was found in eight of these cases, usually in only small amounts. It is of interest in this regard that Mallory (2), apparently on the basis of the post-mortem status, found ascites to be somewhat more

common than jaundice in his "alcoholic" cirrhosis group, whereas in the healed acute yellow atrophy type of cirrhosis, jaundice was more frequently present than ascites.

The gravity of the prognosis seems comparable in Laennec's and post-necrotic cirrhosis. The three most common causes of death in both types of cirrhosis are cholemia, hemorrhage, and intercurrent infection.

SUMMARY AND CONCLUSIONS

1. Ten autopsied cases of post-necrotic (toxic) cirrhosis are reported and their clinical courses compared with those of Laennec's cirrhosis.

2. There is very little apparent difference in the antecedents and courses of the two conditions, and it is unlikely that an accurate clinical differentiation can be made between them.

3. Ascites, and the associated gastro-intestinal symptoms of weight loss, anorexia, nausea and vomiting, are much less prominent in the clinical picture of post-necrotic cirrhosis than in Laennec's cirrhosis. It is questionable, however, whether in the differential diagnosis of an individual case, this statistical differentiation would be helpful.

The authors wish to express their gratitude to Dr. Otto Saphir, chairman of the Department of Pathology, Michael Reese Hospital, who is responsible for the pathological diagnosis in these cases.

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A NEW ANTI-ULCER DRUG: A CLINICAL AND RADIOLOGICAL EVALUATION

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DURING THE past few years research has brought to light many interesting compounds affecting the autonomic nervous system. The isolation of a single compound with specific pharmacodynamic principles frequently proves to be only the beginning, since derivatives are often found to be more important than the original substance. Such has been the case with certain compounds producing functional inhibition in the gastrointestinal tract, among them homologues of Trasentine hydrochloride (1). In expanded studies (2-6) one of these, Ba-5473 (phenylcyclohexyl-oxyacetic acid-diethylaminoethyl-ester-bromomethylate),* has been demonstrated to have sympathetic ganglionic blocking activity, marked gastric antisecretory and antacid properties and to be more effective in preventing peptic ulcer formation in the Shay rat than either atropine or Banthine. On the basis of this information Ba-5473 was administered to laboratory animals for "toleration

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*PROVIDED for this study by the Research Department of Ciba Pharmaceutical Products, Inc., originally as scored 25 mg. tablets, later as scored 10 mg. tablets.

limits" and then to laboratory volunteers for human tolerance before release for clinical study.

This orally effective compound is available in tablet form and in solution for parenteral administration; tablets are practically tasteless if swallowed quickly, and are well accepted by patients. Up to the present Ba-5473 has been given to 24 peptic ulcer patients. A particular routine of observation was devised for each, consisting of roentgenologic examination of the upper gastrointestinal tract prior to treatment, a check series at the end of three weeks, and another series at the end of three months. In six of the patients, after the diagnosis of a peptic ulcer had been made but before treatment, a determination of the total and free acid content of the stomach was made. These determinations were repeated three to six weeks later. In addition, clinical observations were made in regard to relief of pain, muscle spasm, etc.

When clinical trials were begun the dosage was a matter of trial and error. Since it had already been demonstrated that normal subjects could take up to 50 mg. at a single dose, it was decided to begin with one 25 mg. tablet every six hours around the clock. Later experience indicated that this dosage was too high and

REPRESENTATIVE CASE REPORTS



CASE TWO

1. Diagnostic film prior to Ba-5473 therapy. Coarsened gastric rugae, antral spasm and ulcer crater on posterior wall of duodenal cap.
2. 48 hours after beginning Ba-5473 therapy. Gastric rugae less marked; some dilatation of duodenal loop, less deformity of cap.
3. After 3 months still less rugal thickening and no cap deformity.

that it was not necessary to give the medication during the night. The average optimum dose for most of the patients was 10 mg. three times daily and at bedtime, although a few patients required only 5 mg. per dose. The patients were kept on their respective routines for at least three weeks and some for twelve weeks and then the dose was usually halved; observations are being continued as to the adequacy of this maintenance dosage. In addition to their medication the first few patients were restricted to either a soft, bland or Meulengracht diet, as well as being advised to decrease the use of tobacco and alcoholic beverages. Later, however, this regime was changed and the patients were not restricted in any way except to omit barbecue, hot dogs and hamburgers from their diet.

Side effects were encountered, and they were essentially those typical of any parasympatholytic agent, consisting of dryness of the mouth, some epigastric fullness due to gastric dilatation, mild constipation, etc. The side effects appeared to be proportional to the dosage of the drug used, but in our experience those associated with therapeutic dosages of Ba-5473 were less pronounced than those of certain other drugs frequently used in the management of peptic ulcer.

Case No. 2—DBC WMM Age 21.

A diagnosis of peptic ulcer in this man was made elsewhere in 1949, and he was treated with oral medication and a diet for several months. In June, 1950, he had a recurrence and at that time was started on Banthine and restricted diet, with considerable subsequent improvement. In May 1951 he was seen in our emergency room because of nausea, vomiting and



CASE FOUR

1. Diagnostic film: on Banthine therapy, prior to Ba-5473 therapy. Spasm and deformity of cap, with ulcer crater in mid-posterior portion of cap.
2. After three weeks' Ba-5473 therapy. Slight reduction of gastric dilatation; no visible ulcer crater.
3. After three months' Ba-5473 therapy. No ulcer crater visible.



CASE NINE

1. Diagnostic film, prior to Ba-5473 therapy. Ulcer crater posterior (upper) portion of cap.
2. After three weeks' Ba-5473 therapy. Marked dilatation of stomach; no ulcer crater visible.
3. After three months' Ba-5473 therapy. Stomach returning toward normal size. Questionable ulcer crater (none seen on radiologic exam one week later).

epigastric pain; examination elicited marked epigastric tenderness and muscle spasm. The following day x-ray examination showed marked coarsening and thickening of the gastric rugae with antral spasm and a cloverleaf deformity with a definite ulcer crater on the posterior wall of the cap. The patient was then started on 25 mg. of Ba-5473 every four hours day and night along with a puréed diet. Within 24 hours he was completely asymptomatic, and it is of special interest that radiologic re-examination two days later showed a moderate dilatation of the stomach but with less deformity of the duodenal cap and a very definite slowing of both gastric and intestinal peristalsis.

The patient did not return for a checkup in three weeks because of the fact that he was completely asymptomatic. However, he did return for a three months' film, which showed less thickening of the gastric mucosa, no delay in gastric emptying, considerably less duodenal spasm and no deformity or ulcer crater. This patient has been maintained since on

10 mg. four times a day, with a normal diet, and has been completely asymptomatic.

Case No. 4—JB WFM Age 40:

This patient stated that her trouble started in 1930 with episodes of indigestion lasting for about a month each time. Three and a half years ago a positive diagnosis of an ulcer was made by another physician, and during the past year these episodes have been much worse. Three or four months prior to being seen by us she began taking Banthine regularly as well as following a diet rather strictly, but she continued to have much pain and for this took large amounts of baking soda. Examination showed marked epigastric tenderness, and x-ray visualization showed hypertrophic gastritis, antral spasm and marked spasm and deformity of the duodenal cap with an ulcer crater in the mid-posterior portion of the cap. She was then started on 25 mg. of Ba-5473 every four hours; within twenty-four hours she reported by telephone that she was free of pain but was bothered a great deal by dryness of the



CASE THIRTEEN

1. Diagnostic film, prior to Ba-5473 therapy. Ulcer crater at junction of first and second portions of duodenum on posterior wall; considerable adjacent mucosal edema.
2. After three weeks' Ba-5473 therapy. Ulcer crater no longer visible; marked improvement in gastritis.
3. After three months' Ba-5473 therapy. Duodenal cap normal in appearance.



CASE FOURTEEN

1. Diagnostic film, prior to Ba-5473 therapy. Marked antral gastritis; typical cloverleaf deformity of cap, with ulcer crater in upper portion of posterior wall.

2. After three weeks' Ba-5473 therapy. Some antral gastritis still present, but no ulcer crater visible. Note anticholinergic effect upon mucosal pattern of duodenal loop and proximal jejunum.

3. After three months' Ba-5473 therapy. Antral gastritis improved; no ulcer crater visible.

mouth. Dosage was then reduced to 12.5 mg. every six hours and on this she did very well. At the end of three weeks radiologic examination showed some hypo-motility of the stomach and no ulcer crater was seen at that time. The patient was then placed on 10 mg. four times a day and on this continued to do well. At the end of three months x-rays showed gastric emptying to be normal, with less duodenal spasm and no visible ulcer; she was asymptomatic. The patient has continued to take 5 mg. four times daily since that time and has had no recurrence of symptoms.

Case No. 9—WEH WFM Age 59.

This woman had a typical story of peptic ulcer of several

months' duration; physical examination showed marked epigastric tenderness and spasm, while x-rays revealed a small ulcer crater on the upper posterior wall of the cap. Gastric analysis showed 43 degrees of total acid and 29 degrees of free acid. She was started on 12.5 mg. of Ba-5473 four times a day and had no pain after 36 hours. She began to gain weight immediately, but had a great deal of dryness and some constipation; both these complaints improved with reduction of dosage to 10 mg. four times daily.

Three weeks later x-ray showed no ulcer crater and her only complaint was mild constipation, well controlled with mineral oil. At the time of her three months' checkup the pa-



CASE FIFTEEN

1. Film prior to Ba-5473 therapy, showing extensive hypertrophic gastritis, large ulcer crater in duodenal cap, plus so-called "deficiency state" small bowel mucosal pattern, commonly seen in chronic alcoholics and patients with avitaminosis. Patient had been on Banthine therapy for many months because of previous diagnosis of gastric as well as duodenal ulcer. Gastric ulcer not seen at this time.

2. After three weeks' Ba-5473 therapy. No visible gastric nor duodenal ulcer.

3. After three months' Ba-5473 therapy. No peptic ulcer visible; duodenal cap now normal in appearance.

tient was still asymptomatic; gastric analysis showed only 20 degrees of total acid and 10 degrees of free acid. However, x-ray examination showed a questionable tiny ulcer crater; the dosage of Ba-5473 was then increased to 15 mg. four times daily. X-rays a week later showed no sign of an ulcer crater. The patient has continued on 15 mg. four times a day, without significant side effects, and has been asymptomatic since.

Case No. 13—JG WMM Age 31.

This man came into the hospital following dietary and alcoholic indiscretion with severe epigastric pain, nausea and vomiting. Examination showed marked epigastric tenderness and x-ray studies showed a distinct ulcer crater at the junction of the first and second portions of the duodenum on the posterior wall, with considerable adjacent mucosal edema; no obstruction was present. The patient was placed on 10 mg. of Ba-5473 four times a day and after 36 hours had no pain at all. Within four or five days, however, he developed blurring of vision, some nausea as a result of gastric dilatation and urinary retention. Dosage was reduced to 5 mg. four times a day, and on this he had no blurring of vision, no retention, nausea or pain. At the end of three weeks he was again x-rayed and no ulcer crater was demonstrated at that time. He continued on his routine of 5 mg. four times a day and at the end of three months x-ray examination showed the duodenal cap to be normal in appearance.

Case No. 14—WAM WMM Age 42.

This patient came in because of colic-like upper abdominal pain occurring after meals, associated with a great deal of gas and indigestion. Examination showed extreme tenderness and muscle spasm in the epigastrium. X-rays showed rather marked antral spasm, deformity in the duodenal cap and a distinct ulcer crater in the upper portion of the posterior wall. The patient was started on 10 mg. of Ba-5473 four times a day with no restriction of diet, and within 24 hours he was completely asymptomatic. Prior to institution of therapy the patient had a gastric analysis which showed 19 degrees of total acid and 12 degrees of free acid; at the end of the three weeks on Ba-5473 his total acid was 5 degrees and his free acid was zero. X-rays at that time still showed some antral gastritis, but no ulcer crater could be seen; no tenderness was elicited on palpation. Some blurring of vision on 10 mg. four times a day necessitated reduction of this dosage to half that, which was well tolerated. His three months' x-ray examination revealed less antral gastritis and no evidence of peptic ulcer.

Case No. 15—AYB WMM Age 53.

This man was first seen in March 1950 because of very severe epigastric pain. He was admitted to the hospital and x-ray studies showed a gastric as well as a duodenal ulcer. The patient was placed on Bantline and did fairly well on continuous therapy until September 1951, but continued to have some pain. X-rays showed extensive hypertrophic changes in the stomach but no demonstrable gastric ulcer. The duodenal cap, however, still showed a large ulcer crater. The patient was placed on 10 mg. of Ba-5473 four times a day and his pain disappeared completely within 24 hours. Three weeks later he was seen again; x-rays at that time showed no gastric nor duodenal ulcer. Since then the patient has remained completely asymptomatic on 10 mg. four times a day, but has not had his three months' checkup as yet.

COMMENTS

Standard radiologic techniques were used for examinations. The contrast medium employed was pure barium sulphate (Veri-o-pake, G. E.) mixed with tap water, which remains in suspension exceptionally well. No patient was ever given over four ounces of this mixture, and it was only rarely that over two and a half ounces were needed.

In the conduct of radiological examinations of the gastrointestinal tract, it is generally agreed that fluoroscopic examinations are our most valuable single method of accessory clinical study today. Radiographic films are

of invaluable adjunctive aid and serve to afford permanent records of our fluoroscopic findings.

Within very recent years radiologists have been afforded the opportunity to observe and study patho-physiology of the gastrointestinal tract in relation to certain drugs, particularly those having parasympatholytic action. The resultant changes are not unlike those occurring in vagotomized patients except that the latter show more marked variation of gastrointestinal tract dilatation and hypomotility. We have noted that following vagotomy gastric ballooning at times attains enormous proportions, with delayed emptying and its accompanying subjective symptoms. At other times the vagotomized stomach shows only minor degrees of enlargement, though there is generally a uniform delay in gastric emptying time.

Banthine bromide, an anticholinergic preparation, is one such drug currently employed in practice for patients with peptic ulcer. Within a few hours after its administration barium studies show a slowing of the peristaltic activity in the upper gastrointestinal tract, followed later by demonstrable gastric dilatation. Gastric emptying time will vary from normal to markedly delayed, but some delay is usual.

In the series of patients treated with Ba-5473, those first studied radiologically had been started on dosages above those later found effective and well tolerated. We observed rather marked early gastric dilatation without much change in emptying time, even before any significant alteration in peristaltic activity was noted. The hypertrophied gastric rugae so frequently noted in the peptic ulcer patient remained unchanged for about three weeks in most of these patients.

The loop of the duodenum and upper portion of the jejunum also appeared to dilate slightly in the early days of the drug's administration, but at no time was there any evidence of pooling or segmentation of the bowel. Some unusual prominence of the mucosal pattern was occasionally noted in the upper bowel.

An observation of great interest was the apparent adaptation of the upper gastrointestinal tract to maintenance dosage of the drug. Within one or two weeks gastric dilatation practically disappeared and emptying time was approximately normal. This adaptation was observed even without reduction of dosage; only other side effects necessitated such reduction in certain instances.

Constipation did not constitute a problem with the administration of Ba-5473 after proper adjustment of dosage.

RESULTS

This report records the successful use of a new, well tolerated parasympatholytic agent, Ba-5473, in 24 patients having a definite diagnosis of active peptic ulcer, with x-ray visualization of the crater obtained in each case except one. In that case there were all the clinical and radiological signs of recurrent activity in a peptic ulcer except for a demonstrable crater.

Nearly all these patients had been on an anti-ulcer regime prior to treatment with Ba-5473 and several were being actively treated at the time that they were studied by us and an active ulcer was found.

With one exception (case 2), these patients were rechecked radiologically and clinically at the end of three weeks' therapy. Case 2 gave every clinical indication of marked improvement, and nineteen of the remaining twenty-three patients showed complete healing of ulcer craters at that time; two patients are not yet due for three weeks' checkup. In one of the two cases showing incomplete healing by x-ray after three weeks' therapy the ulcer was reduced in size and was completely healed at seven weeks. The other showed reduction in size, with symptomatic relief, at three weeks, then complete ulcer healing at three months.

With no exceptions this group of patients became free of ulcer symptoms within twenty-four to thirty-six hours after initiation of treatment with Ba-5473, although in five cases moderate increase in dosage was required later to permit complete ulcer healing or control recurrence of symptoms.

Seventeen patients have been restudied clinically and radiologically at the end of three months' therapy; all were asymptomatic and showed complete ulcer healing (one patient refused to return for his checkup because he felt entirely well). The remaining patients will be rechecked at the appropriate time.

Six of the total of eighteen patients had one pre-treatment determination of gastric acidity and another after at least three weeks' therapy. In each case there was a significant reduction in total and free acid levels; in two free acid was reduced to zero, while one showed no free acid before or during therapy.

Several of the patients in this series have now been taking maintenance doses of 5 to 10 mg. of Ba-5473 four times daily for as long as nine months. Up to the present there have been no ulcer recurrences and most of the patients are symptomatically well. The only complication observed has been the occurrence of sudden pyloric obstruction requiring gastro-enterostomy in a patient who had taken the drug for eight and a half months. At the time of operation no active ulceration nor duodenitis was observed; firm scar tissue had caused the obstruction.

ADDITIONAL USES

The gastric antisecretory effect of Ba-5473 has also been studied in eight patients having severe hypertrophic gastritis without peptic ulcer (proven by x-ray). Several of these patients had been very resistant to more usual types of treatment and without exception obtained dramatic and lasting relief of pain from the administration of Ba-5473.

The drug was also given to one patient having a duodenal diverticulum with recurrent episodes of right upper quadrant pain. Previous therapy with atropine had provided only partial relief, but during seven months' treatment with Ba-5473 she has had no attacks of pain.

The drug was also given to two patients with spastic colitis and one patient with severe asthma (because of its bronchial spasmolytic action) without any relief of their symptoms with the dosage employed.

SUMMARY

1. Clinical data upon use of a new parasympatholytic agent, Ba-5473 (Ciba), are presented.

2. Twenty-four patients so treated had radiologic confirmation of clinically diagnosed peptic ulcer; eight more had hypertrophic gastritis without peptic ulcer and another had duodenal diverticulitis.

3. With individual adjustment of dosage at 5 to 15 mg. four times daily all these patients obtained complete symptomatic relief. Acute symptoms were relieved in every case within 24 to 36 hours after beginning therapy; it was not necessary to continue dietary restrictions beyond the initial stage of treatment, if used at all. Average maintenance dosage is 5 to 10 mg. four times per day.

4. No significant side effects were observed after individualization of dosage at 5 to 15 mg. four times daily.

5. Radiologic evidence of ulcer healing after three weeks' therapy was obtained in nineteen of the twenty-four cases. One patient was not checked thus at three weeks, but was asymptomatic then, and after three months x-ray examination showed that the ulcer had healed. Two patients are not yet due for three weeks' restudy.

One patient showed reduction of the ulcer crater at three weeks, then complete healing at seven weeks.

One patient showed reduction of ulcer size after three weeks with complete healing at three months.

6. One patient having duodenal diverticulitis and pain previously uncontrolled by atropine has been asymptomatic during seven months' treatment with Ba-5473.

7. Two patients with spastic colitis and one with bronchial asthma obtained no relief from acute administration of Ba-5473.

8. It is believed that the parasympatholytic agent Ba-5473 warrants further study as an agent of real potential in the management of peptic ulcer, hypertrophic gastritis without ulceration and other spastic conditions of the upper gastrointestinal tract.

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HYPERCHOLESTEROLEMIA AND SENESCENCE

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"YOU THAT are old consider not the capacities of us that are young; you do measure the heat of our livers with the bitterness of your gall" (1). The Bard, in a way, anticipated the advances in biochemistry which now indicate the importance of the liver in the aging process.

There are a score or more liver function tests which depend for their interpretation on the ability of the liver to control the concentration of some normal constituent of the blood or to remove some foreign substance introduced into the circulation (2). Other tests demonstrate the patency or compromising of the bile passages. Except for this latter group, most of the tests have so little clinical value that they have largely fallen into disrepute and desuetude. A large part of the liver parenchyma can be functionally or even anatomically destroyed before any significant impairment of hepatic function can be demonstrated by any chemical test.

Lipid metabolism is of the utmost importance to the body economy. Yet we can get along in a reasonable state of health with very wide variations in the concentrations of the blood lipids (3). Apparently, however, the variation in the proportions of the various components is very much less than that of any one of them or of their total (4). This, of course, refers to the blood lipids in the fasting state for most of them rise post-prandially, especially after a fatty meal (5). On the other hand, the total blood (or serum) cholesterol is unique among lipids in that the diurnal variation is practically nil (6). This was true even after the addition of 20 grams of pure cholesterol to a test meal (6).

This constancy of proportion is most fortunate for we can watch the progress of any case by determination of but one constituent. For this purpose, the total serum cholesterol affords many important advantages. The estimation can be made from 0.1 mil of serum which can be secured by finger prick (7). The apparatus is simple and inexpensive. The technique requires minimal laboratory skill and experience to obtain reproducible results. The patient requires no preparation and the test can be done at any time of the day. More elaborate analyses would make the observation of patients economically prohibitive. Recognizing that we have cheerfully sacrificed scientific completeness on the altar of expediency, we may use this single determination as a first approximation to the truth that is entirely adequate for clinical purposes.

The healthy liver is well loaded with glycogen. In a number of pathological states, the liver glycogen is replaced by fat. Fatty livers have been produced experimentally by prolonged excessive feeding of lipids, especially cholesterol (8), administration of alcohol (9), feeding of vitamin B factors in enormous amounts (10), pancreatectomy (11) and poisoning by various substances such as chloroform, phosphorus, benzol,

etc. (12). Insufficient feeding of protein can also produce fatty degeneration of the liver (13).

The fatty liver loses its ability to metabolize lipids and a prominent effect is an increase in the total serum cholesterol with a diminution in the proportion of esterified cholesterol (14). Clinically, hypercholesterolemia is found, *inter alia*, in nephrosis (15), hypothyroidism (16) and diabetes mellitus (17).

In their natural state, herbivores ingest infinitesimal amounts of cholesterol. Anitschkow fed cholesterol dissolved in vegetable oil to rabbits, causing their serum cholesterol to rise (18). He produced lesions in their arteries indistinguishable from human atherosclerosis. For many years, abortive attempts were made to produce similar lesions in carnivores and omnivores. Recently, however, by feeding large amounts of cholesterol with thiouracil (to induce hypothyroidism) to dogs, it was possible to produce atheromata (19).

It has been thought that something peculiar to the physiology of herbivores made them susceptible to atherosclerosis when they were fed cholesterol. However, atheromata have been produced in both rabbits and dogs by injecting colloidal suspensions of such substances as polyvinyl alcohol, pectin, gum arabic and methylcellulose intravenously (20). It now seems unnecessary to invoke any special mechanism to explain the rabbit's susceptibility to cholesterol. His metabolic processes need not be adapted to handling this substance and any excess precipitates out as any solute will from a supersaturated or colloidal solution.

The connection between hypercholesterolemia and human arteriosclerosis is still controversial. However, a significant correlation between the former and coronary disease has been noted (21).

The conditions previously mentioned that give rise to hypercholesterolemia do occur in humans. We have diabetics, nephrotics and many persons whose metabolic rates are on the low side, although we often include them among normals by setting the accepted limits low enough. The parlous state of the world situation has led many hitherto abstemious people to find surcease in alcohol, the consumption of which is increasing at an appalling rapidity. Dietary indiscretions are only too common. The increased cost of meats makes adequate protein intake prohibitive for large sections of the population. If that were not bad enough, the blatant blatherings of the numerous food faddists have influenced many otherwise sane people to limit their proteins below the capacities of their purses. And who has not heard the radio's nutrition "experts" who continually press the consumption of excessive amounts of the vitamin preparations they exploit over the air waves and in their publications for the laity?

Fortunately, we now have at our disposal a number of "lipotropic substances" that have a salutary effect on impaired lipid metabolism. These have been known

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chemically for many years and their physiological action in promoting the metabolism of lipids by the liver has been recognized for about twenty years (22, 23, 24). Until recently, they remained laboratory curiosities and their therapeutic application would have been prohibitively costly. Now that the demand has made them generally available, they have been used to avert the deleterious effects on lipid metabolism of the noxious agents and processes mentioned above (25). Indeed, many a case of actual cirrhosis of the liver has been snatched from an internally watery grave by their judicious use. They are normal participants in the body economy and, by insuring a sufficiency of them to an overtaxed liver, we can restore its ability to metabolize lipids.

Unfortunately, the problem is complicated by the fact that there is no agreement as to what is the normal cholesterol level. The most generally accepted limits are 150 to 250 milligrams per 100 cubic centimeters (26). The optimum must be fairly close to the lower value because the Chinese, who are singularly free from arteriosclerotic diseases have cholesterol levels around 100 mgs. per 100 cc. (27). Furthermore, the different methods of analysis are discordant. They all depend on the extraction of a suitably prepared sample with a cholesterol solvent. Most of the methods suffer from incomplete extraction and the values tend to be too low. The methods of analysis employed in this work gives the highest values when compared with other standard procedures in a large series of comparative analyses because complete extraction is inherent in the method (7). It is felt that the "normal" should not be significantly greater than 200 mgs. per 100 cc.

Hypercholesterolemia can be combatted by rigorous exclusion of cholesterol from the diet (28). In fact, the low cholesterol levels of the Orientals is probably due to their adaptation to a preponderantly vegetarian diet. However, for us, these diets are most onerous. Furthermore, the body can manufacture cholesterol from such ubiquitous substances as water and acetic acid (29) and the effectiveness of so monotonous a regimen is open to question. The desirability of complete avoidance of cholesterol intake is highly questionable for that substance is probably the precursor of the vitally required adrenal cortical and sex hormones (30). It seems more physiologic to permit an adequate intake of the substance and to insure its more effective utilization by keeping the liver healthy.

With restoration of hepatic sufficiency, the serum lipids are reduced to normal values. By following the level of the serum cholesterol, we can gauge the effectiveness of treatment. In many cases, it was possible to make other objective observations that indicated a return toward health.

The lipotropic product used in this investigation was "Methischol." It contains the three lipotropic agents, METHionine, InoSitol and CHOLine, together with liver extract and vitamin B-12. Since there is no way of estimating adequacy of dosage, each patient was started with three of the capsules after each meal, making a total of nine a day. After satisfactory reduction in the cholesterol level had been attained, the

dosage was reduced to but one capsule after each meal. The patients were advised to continue with this reduced intake indefinitely.

The only other routine medication was a single multi-vitamin capsule before breakfast. Some time ago, an editorial in the *Journal of the American Medical Association* urged that vitamins be purchased in the grocery, not the drug store. True enough. But our complex distribution system requires our foods to be refined to make them less perishable. In the preparation for the consumer, a significant part of the vitamins is removed. By taking but one of the approved vitamin capsules daily, we insure an adequate supply without running the risk of excessive intake.

Eighty-six patients with hypercholesterolemia were investigated. Of these, seventy-four had exceeded the allotted three score years and ten. Only one of the other twelve was younger than sixty years. Eleven cases will be reported in varying detail since they presented features of considerable interest. Each of them has been more or less duplicated by others which need not be given more than this cursory mention.

CASES

I. M. M. F., male, 74. This patient was first seen on December 14, 1948 after he had been ill for several months with marked prostration and abdominal swelling. The liver was a hand's breadth below the costal margin to percussion. The edge could not be felt because of the enormous abdominal distension and ascites. The umbilicus was completely obliterated. The pulse rate was 60 (which, as he said, had been so throughout his life). The blood pressure was 104/80. No other abnormalities were noted. Abdominal paracentesis yielded 9 liters of clear yellow fluid containing 6.8% protein (612 Grams!). His blood contained—

Cholesterol	365
Urea Nitrogen	24
Uric Acid	3.6
Calcium	9.2
Glucose	78 mgs. per 100 cc.

The Icterus Index was 12; the Van den Bergh test showed Direct positive; Indirect 2 units.

A diagnosis of hepatic cirrhosis was made in view of these findings and his long history of liberal consumption of alcohol. He was treated according to Patek and Post's recommendations (31) with a high vitamin, high protein diet (to compensate for the enormous drain of serum proteins into his ascitic fluid). He was also given a daily injection of vitamin B complex fortified with 200 milligrams of thiamine chloride dissolved in 10 cc. of "Calphoson." This vehicle was used as the diluent to render the injections somewhat less painful and to raise his serum calcium (32). In addition, he was given 9 capsules of methischol and 5 grains of thyroid extract ("Prolid") per day.

His general condition did not warrant the determination of his basal metabolic rate. Furthermore, no reasonable accurate estimation of his weight could be made for there was no way of allowing for the weight of his ascitic fluid. The B. M. R. was therefore roughly estimated by Read's formula (33)—

$$\begin{aligned} \text{B. M. R.} &= 0.683 \times (\text{pulse rate} + 0.9 \times \text{pulse pressure}) - 71.5 \\ &= 0.683 \times (60 + 0.9 \times 24) - 71.5 = -16\% \end{aligned}$$

Past experience having shown that one grain of the preparation of thyroid used per day would raise the metabolic rate by 4%, 5 grains was estimated to be the correct dose.

His abdomen continued to fill with ascites and he had to be tapped at increasingly frequent intervals until he required the removal of 12 to 15 liters every three weeks. The fluid

*Furnished through the courtesy of the U. S. Vitamin Corporation.

spread so that his legs became edematous clear to the soles. On February 20, 1949, the ankle edema had vanished almost over night. An abdominal paraecetesis had been contemplated but it was felt that he was beginning to reabsorb the fluid and he was urged to withstand the discomfort of his abdominal distention in the hope that the fluid would leave that region too. On February 23, 1949, that hope was realized and no further tapping was ever necessary. The vitamin injections were reduced to 3, then 2 and, finally 1 a week during the next two months.

On May 2, 1949, his blood findings were—

Cholesterol	222
Urea Nitrogen	16
Calcium	10.9
Icterus Index	5
Van den Bergh	Direct negative; Indirect 0.5 unit.

His general condition had improved sufficiently to make possible and significant the determination of his basal metabolic rate. It was +6%, indicating that his thyroid dosage was correct.

His medication was simplified to one multivitamin capsule and 5 grains of thyroid each morning and one methiscol capsule after each meal. Throughout his illness, he utterly refused to abstain from alcohol. He did moderate his drinking and probably consumed less than 6 ounces of whiskey a day. This intake began to rise as he began to feel better and was able to visit his old cronies. He had retired from the presidency of a large corporation and he used spirits as a refuge from boredom. Yet, he got along fairly well for about a year. By March, 1950, his liquor consumption had risen to more than a quart a day! He became progressively feebler, unsteady in his gait and thickened in his speech. However, there was no return of ascites. The dose of methiscol was tripled.

He improved somewhat for a few weeks. Then he became lax in taking his medication. He ate almost no real food, subsisting largely on liquor. He went downhill rapidly and, on July 1, 1950, he went into a stupor from an obviously wet brain.

Heroic measures were instituted. He was given intravenous injections of 50% glucose and large intramuscular injections of vitamins daily. Fortunately, it was possible to withhold liquor. After 10 days of a condition fluctuating between moderate stupor and profound coma, he began to improve. By the end of the month he had recovered sufficiently to leave his home.

Incidentally, during the height of his illness he developed cracks at the corners of his mouth and "shark skin" at the angles of his nose. He was given 5 mgs. of riboflavin and 100 mgs. of niacinamide three daily for a month (in addition to his other medication). The lesions cleared up completely and a curious affliction of the skin of his shins for which he had been treated by almost every prominent dermatologist during the past twenty years also healed. Obviously, he had had a mild pellagra which had escaped recognition.

On October 17, 1950, his serum cholesterol had fallen to 194 mgs. per 100 cc. The methiscol capsules were again reduced to but three a day. Unfortunately, the good news called for celebration and his thirst again knew no bounds. Before he could slip back into stupor, he was again placed on the rigid regime of vitamin injections and increased dosage of the lipotropic medication. In a fortnight, the treatment staved off the threatened collapse.

When he felt better, the riot act was read to him and he promised better cooperation. He has kept his promise to limit his whiskey intake to four ounces a day. It is felt that it is better to permit him a reasonable consumption of alcohol than to attempt the impossible task of making him the only teetotaler in his business and social milieu. Now, for more than a year, his health has been excellent. He is alert and vigorous. His appearance belies his age and past history. He continues to take three methiscol capsules and a vitamin capsule each day. He requires no medical attention, the only opportunities for observation being the frequent

purely social meetings, which are a delight—thanks to his incisive wit and intelligent observations.

COMMENT. This startling case shows the efficacy of the lipotropic substances in mitigating the toxic effects of alcohol on the liver and circulation. While he has been taking these drugs he has given no evidence of liver damage although he, at times, consumed many times as much alcohol as he had ever taken—enough to cause cerebral edema. The almost unexpected recovery must be attributed, at least in part, to the fact that the large and prolonged intake of these agents had prevented complete metabolic dissolution.

II. J. M. F., male 74. In February, 1949, he complained of dyspnea and swelling of his ankles. His heart was not significantly enlarged. The sounds were of good quality, regular and free from murmurs. His blood pressure was 160/80; the pulse rate was 88. The electrocardiogram was essentially normal. The liver edge could be felt three fingers' breadth below the costal margin. The ankles were edematous and there was a small amount of abdominal fluid.

He was digitalized and then maintained with 1 cat unit of digitalis per day. Within two weeks, his pulse rate fell to 76 and his breathlessness, ankle edema and slight ascites vanished. But the liver edge did not regress. Therefore, his serum cholesterol was determined. It was 328 mgs. per 100 cc. He had always been a finicky eater and could not be held to any dietary regimen. His treatment was therefore confined to 9 methiscol and 1 multivitamin capsules a day, plus, of course, his digitalis. This treatment was apparently adequate for his liver edge retreated to the costal margin within a month. In April, 1949, the serum cholesterol was 22 mgs. per 100cc. His lipotropic medication was reduced to three a day.

He got along quite well for about a year. In the early part of 1950 he began to be annoyed by the symptoms of prostatism which gradually became worse. In May, 1950, he had a severe upper respiratory infection. The added burdens of the infection and the urinary retention were too great for his impaired cardiac reserve and, one night, he suddenly went into heart failure for which it was urgently necessary to perform a phlebotomy of 1000 cc. He was kept in bed and compensation was restored in a few days. However, the enforced inactivity and the mercurial diuretics which had to be administered led to a complete urinary retention and it became utterly necessary to subject him to prostatectomy. He withstood the operation very well. However, the overzealous administration of fluids by continuous intravenous drip ordered by the surgeon over the objection of his medical advisor exacted its toll on the patient's impaired cardiac reserve and he again went into heart failure. Another phlebotomy of 500 cc. and the discontinuance of the unnecessary (and, indeed, contraindicated) therapeutic regimen restored compensation and recovery was thereafter uneventful.

Advantage was taken of his hospitalization to determine the serum cholesterol. Since it was only 186 mgs. per 100 cc., he was grudgingly permitted to discontinue his methiscol capsules. He always objects to any medication.

He gradually improved in strength and was able to take a trip to California during the Summer. After his return to New York, he seemed to be in excellent health for a while. In October, 1950, his health failed precipitously. His appetite, which had never been hearty, almost vanished. He became feeble. His voice, which had always been deeply resonant, took on the quavering quality of the tired old man he had become. He is a famous artist but he lost all interest in his work and refused commissions for which he no longer had the strength or interest to execute.

Only because all other investigation shed no light on his difficulties, his serum cholesterol was determined on November 17, 1950. It had risen to 348 mgs. per 100 cc. He was again given the lipotropic capsules. His strength began to pick up in but two weeks. By the end of the year, he had regained the 20 pounds that he had lost. He resumed painting—his work having been successfully exhibited last year.

Several determinations of his serum cholesterol showed that the level has remained between 200 and 210 mgs. per 100 cc.

He has remained in excellent health for more than a year. Unfortunately failing vision has prevented him from working at his art for the past few months.

COMMENT. The conclusion that the correction of his hypercholesterolemia enabled him to withstand the rigors of the operative procedure and the post-operative man-handling seems inescapable. In retrospect, we can now see that it was a mistake to stop his lipotropic medication for his subsequent failing health was accompanied by the demonstrated rise in serum cholesterol. When the proper therapy was reintroduced, his health returned.

III. D. A., female, 78. Her past medical history includes panhysterectomy for carcinoma of the fundus uteri in 1925, nephrectomy for stag horn calculus in 1946 and mild diabetes mellitus since 1935. For several years, she complained of pains and aches in her legs which always felt cold. She had to wear woolen stockings at night in order to sleep. During the cold months, she could never go out of doors unless she wore two pairs of stockings.

In 1949, her legs gave her trouble even during the warm weather. She had great difficulty in walking up even a few steps. Oscillometry showed deflections of but 2 on the right calf and 4 on the left (Collens Oscillometer). The serum cholesterol was 420 mgs. per 100 cc. She was given 9 methiscol capsules a day. During the Winter of 1949-50, she could, for the first time, in many years, wear but one pair of Nylon stockings throughout the entire cold period, going out in all but the most inclement weather. In April, 1950, her serum cholesterol was 262 mgs. per 100 cc. and the oscillometric readings had risen to 5 on the right and 6 on the left calf. Her medication was reduced to one third.

In June, 1950, she had daily attacks of coronary spasm without any substantiating electrocardiographic findings. It was felt that these attacks were induced by her gall bladder for they always occurred postprandially and she was known to have had gall stones for many years. In spite of her coronary symptoms and advanced age, she courageously submitted to cholecystectomy from which she recovered without incident.

COMMENT. The high serum cholesterol was probably due to the long history of gall bladder disease and diabetes, both of which are often accompanied by hypercholesterolemia. It is felt that the preliminary treatment with the lipotropic agents materially aided her in recovering from the operation at her advanced age. She manages her home and can walk considerable distances and can climb moderate flights of stairs with comfort.

IV. B. S., female, 65. She had been a diabetic for many years. In March, 1948, she was seen for the first time when she had dry gangrene of the right big toe. The oscillometric readings were 1 on the right and 3 on the left calf. Serum cholesterol was 395; blood glucose was 365 mgs. per 100 cc. A casual specimen of urine contained 6% sugar. She was ordered to bed and told to keep her feet under a cradle to keep the toes warm. She had been taking insulin sporadically for several years but had given her physicians little or no co-operation. She ran true to form and did not stay off her feet. However, her daughter forced her to take methiscol regularly. When she returned, a month later, her toe had healed completely. The oscillometric readings were 4 on the right calf and 3 on the left. The serum cholesterol was 280; the blood sugar was 334 mgs. per 100 cc. She did not take any insulin during the entire period. A twenty-four-hour urine contained 116 grams of glucose! She has been seen from time to time since then when she accompanied her daughter to the office but has utterly refused to be examined or even interviewed, claiming that she feels entirely well. Her daughter has seen to it that she takes the methiscol capsules.

COMMENT. This patient made a recovery to which her lack of cooperation did not entitle her. Since the only medication or any other therapy she followed was

the lipotropic capsules, they must have effected the cure.

V. S. F., female, 72. Her initial complaints were pains in her legs and great fatigue. Oscillometric readings were 4 bilaterally. The serum cholesterol was 365 mgs. per 100 cc. After medication for three months, the oscillometer needle gave deflections of 6 on the right calf and 8 on the left. The dosage was reduced to one capsule after each meal. Two months later, the findings were substantially the same. However, she now complained of eructations following her medication. She had some nausea. The manufacturer was kind enough to furnish the drug in enteric coated tablets which she tolerates very well. Several other patients had to be given the tablets for the same reason.

VI. J. F., male 47. He works at a battery of telephones in an international brokerage office under very great tension. He had attacks of precordial pain for which he consulted five cardiologists during 1948. Each took an electrocardiogram none of which demonstrated any abnormalities. He was prescribed an assortment of sedatives without any relief. In March, 1949, his serum cholesterol was 295 mgs. per 100 cc. After three months under treatment with lipotropic capsules, the attacks all but disappeared and his serum cholesterol had fallen to 232 mgs. per 100 cc. After another two months, the level was 206 mgs. per 100 cc. and he was entirely relieved of his complaints. He has been taking 3 capsules per day since then and has not had any precordial distress for more than two years in spite of his nerve-racking employment. He does, however, require an occasional sedative after a particularly severe day.

VII. J. P., male, 63. In October, 1948, he had an attack of acute coronary thrombosis for which he was treated with the standard six weeks of bed rest. In January, 1949, he attempted to resume his employment as an outside salesman but he could not drive around without suffering from substernal distress and breathlessness. His cholesterol was 280 mgs. per 100 cc. After medication for three months, the level fell to 212 and he has been able to perform his duties without too much difficulty.

VIII. S. D., female, 86. For a few years, she found it increasingly difficult to walk. Then, she had failure of memory and, at times, did not even recognize members of her family. Her serum cholesterol was 312 mgs. per 100 cc. The oscillometric readings were 3 on both calves. After five months of treatment, her serum cholesterol was 270 mgs. per 100 cc. The oscillometric readings were unchanged. Her mental deterioration became so obvious that her children had to send her into an institution for custodial care. After three months, she improved sufficiently to return to her own home and was alert enough to take care of herself with only minimal assistance from her daughters who took turns in looking in on her at least once each day. Her serum cholesterol was now 222 mgs. per 100 cc. The oscillometric readings were 5 on the right calf and 6½ on the left. She continued on the medication for a little more than a year. Then she had a cerebral hemorrhage from which she died after four days.

COMMENT. We now see that she could not be trusted to remember to take her medication during the early part of the treatment. When regularity of medication was assured in the nursing home, her improvement was truly amazing. She became quite vigorous and alert. The mystery was cleared up when her family discovered the capsules which had been ordered for her when treatment was started. An unopened package was found on the top shelf of a closet where she habitually kept her few most prized belongings and mementos of her long life.

IX. M. I. M., male, 73. This man manages an office for an out-of-town factory. He must travel around the city, carrying a very heavily loaded brief case. He found great difficulty in walking with his burden. His serum cholesterol was 365 mgs. per 100 cc. His oscillometric readings were 5 on the

right calf and 2 on the left. His left leg had tired more easily than its fellow. After a few weeks, he noticed greater vigor in his stride. After two months of treatment, the oscillometric readings had risen to 15 on the right and 11 on the left calf! The serum cholesterol had dropped to 245 mgs. per 100 cc. He has continued with medication in reduced dosage for two years, performing labors that would tax the energy of a much younger man. The serum cholesterol has hovered around 200 mgs. per 100 cc. on several examinations.

X. S. B., female, 69. For several months, she complained of tingling in her legs that would awaken her after a few hours of sleep. She got some relief by taking hot baths which would enable her to rest for a few hours. For several years, she had been annoyed by severe tinnitus. She could follow her heart beat by the whirring sounds in her ears. This gradually became worse and finally troubled her in the day time as well as by night. Her serum cholesterol was 312 mgs. per 100 cc. The oscillometric readings were 5 on the right calf and 4 on the left, which gave her more trouble. After three months on the enteric coated tablets (she had eructations from the very first dose of the capsules) the cholesterol dropped to 233 mgs. per 100 cc. The oscillometric readings were 6 bilaterally. Her "drawing" sensations stopped within two weeks of the start of the medication. After a month, the tinnitus did not disturb her. While she still could hear the noises if she directed her attention to it, they were not loud enough to disturb sleep.

COMMENT. It is difficult to be certain that so subjective a symptom as tinnitus could be relieved enough to permit sleep, especially since she no longer had the aches in her legs that would have been sufficient by themselves, to account for her restlessness.

XI. D. K., female, 64. For many years, she has had malignant hypertension of alarming magnitude. Her systolic pressure has varied between 260 and 380 mm. Her diastolic pressure has not been below 100 mm. for more than five years. It has reached 160 on many occasions. In 1947, she had a proven coronary thrombosis for which she remained in bed for about two months. Every four or five months, it is necessary to remove at least 500 cc. of blood by phlebotomy to relieve her pounding headaches. When her pressure gets very high, she becomes hoarse because the dilated aorta tugs on the recurrent laryngeal nerve. After taking digitalis for a few days, this symptom has always disappeared. In September, 1949, her serum cholesterol was 255 mgs. per 100 cc. She was given methiscol for three months without the slightest effect on her blood pressure or the cholesterol level. She said that she felt better while taking the capsules but this was probably psychic for she always complains less when any "new" medication is tried. She continued with the capsules for another three months. Since there was no change in either her blood pressure or cholesterol level (which was not particularly high) the treatment was abandoned. Incidentally, at one time she tried the rice diet for six months but her pressure remained entirely unaffected.

DISCUSSION

In this potpourri of apparently entirely unrelated cases, we can discover one common denominator—hypercholesterolemia. Indeed, that is the one indication for treatment with the lipotropic agents. This therapy was uniformly successful in reducing the hypercholesterolemia. And, *pari passu*, there was amelioration of the symptoms attributable to arteriosclerosis.

Undoubtedly, the other blood lipids were reduced along with the cholesterol because of their more effective utilization by the liver. This leads to the attractive hypothesis that, in all these variegated cases, we had impairment of lipid metabolism with changes in the liver varying in degree from frank cirrhosis to a sub-clinical fatty infiltration that would defy detection by any of the available liver function tests.

With restoration of hepatic sufficiency we approach

isolepemia. Perhaps this improves the circulation by at least retarding the deposition of atheromatous plaques. The fact that so many of the symptoms of advanced arteriosclerosis have been reduced in severity suggests that there might even be some reversal of the pathological process, but it is difficult to see how this could be substantiated.

It might appear to be an oversimplification to search only for hypercholesterolemia in treating the ravages of age. However, the successful treatment of so many cases with manifest arteriosclerosis has led to the routine of determining the serum cholesterol in every patient over the age of 40. Whenever the level is significantly over 200 mgs. per 100 cc., lipotropic medication is given in the smaller dosage as a preventive measure. It is far too early to evaluate the effect. Since the lipotropic substances are normally present in the body they probably can do no harm and they might stave off the effects of aging. Many of the patients so treated and who never had any symptoms of arteriosclerosis reported that they felt better and could undertake sustained effort with less fatigue. However, this purely subjective observation must be evaluated with great reservation.

Having observed these striking and dramatic clinical effects, it is difficult to maintain enough scientific objectivity to restrain one's enthusiasm. We may have, in these lipotropic substances, an "anti-senescence factor" for many of these patients were saved from obsolescence and were enabled to continue in useful pursuits. The sociological implications should be kept in mind for their indicated use might enable families to keep their aged parents at home instead of dumping them on the scrap heap of institutional vegetation.

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FECAL IMPACTION

REPORT OF A CASE DUE TO WILD GRAPE SEEDS AND ELDERBERRY STEMS.

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FECAL IMPACTION is not a rare disease entity but very little about it is found in the American literature. Bockus says, "Bran and other very fibrous foods are potential sources of danger in some patients." Benson and Bargen are of the opinion that, "Roughage such as bran, psyllium seeds or unusually rough food eaten in time of need or on some other unusual occasion often causes fecal impaction." We are reporting a case of fecal impaction due to eating wild grapes and elderberries which bears out their opinion.

Medications have been implicated as etiological factors in the production of fecal impactions. Schwade reported a case of enteric coated pills as a cause. Fisher reports a case of intestinal obstruction in a female who for several months prior to the obstruction had been taking a spoonful of psyllium seeds daily with the ingestion of very little water. At surgery a grossly distended ileum was found, with an impaction of the seeds ten inches proximal to the cecum. He concludes that those substances are dangerous, especially in elderly people. Wand has found that hygroscopic gum laxative can cause fecal impaction and reports the case of a 68-year-old male with impaction due to dehydrated Saraka. Again, this patient had been taking the preparation with very little water. We cannot overemphasize the need of an adequate water intake when taking preparations of this sort.

Not in the true sense a medication, but certainly a

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medically produced situation is the fecal impaction seen following barium enema. We have all had the opportunity of breaking up a fecal impaction following the use of barium in x-ray procedures, and are well aware that it can and does occur.

Carmel, in an excellent discussion of the problem of fecal impaction lists the etiology under three groups:

"1. Those factors which delay the passage of fecal material through the colon.

"2. Those factors which increase the consistency of the feces, and

"3. Those factors which cause a diminution in the usual quantity of mucous produced by the mucous membrane of the large intestine."

Our case would fall in group 2. Another factor in our case, as mentioned by Bockus, was the presence of an anal ulcer. "An anal ulcer may predispose to impaction of feces because of the occurrence of pain when defecation is attempted." From the history of intermittent anal pain and bleeding and the physical findings we feel that our patient had the anal ulcer prior to the impaction, and as such it played an important part in the production of the fecal impaction. The thrombotic combined hemorrhoid in the left lateral position may have been a factor, but most likely the thrombosis had its origin in the trauma incident to the attempt to pass the seeds and stems.

The development of diarrhea in fecal impaction has been emphasized many times and often is a confusing symptom. We hesitate to consider impaction when the

presenting symptom is diarrhea, but often a persistent diarrhea will be the only complaint in a long standing fecal impaction. Our case illustrates this, as he at first had an increasing constipation and later developed a diarrhea, spending all of one day and a night in the bathroom.

Fecal impactions can reach enormous proportions. May and Torre report the case of a female with progressive enlargement of the abdomen over a period of two years. She reported no bowel movement for one and one-half years, but the patient was a mental defective and the history of no bowel movement for six months, as reported by the family, is probably more accurate. The abdomen was enlarged to the size of a term pregnancy and a diagnosis of large ovarian cyst was made. At surgery a midline incision was made and a large, firm mass that had the appearance of an ovarian cyst presented itself. A trocar was inserted to draw off the cyst fluid, but only inspissated feces filled the trocar. The sigmoid was enormously dilated with feces and five gallons of inspissated fecal material was removed. The patient made an uneventful recovery. The authors feel that this was a true impaction rather than a megacolon.

Fecal impaction can present a confusing diagnostic picture and often the differential surgical diagnosis is difficult. Mullarkey discusses the surgical significance of fecal impaction and presents several cases where the impaction simulates an acute surgical abdomen and erroneous diagnoses of carcinoma of the sigmoid, tubo-ovarian mass, and acute appendicitis (child) were made. He feels that fecal impaction should always be considered in the differential diagnosis of the acute surgical abdomen. Carmel also reports several impactions that had surgical exploration. Our case is again illustrative as the patient was originally seen by the proctology service as a possible bowel malignancy with obstruction.

On occasion the presence of a fecal impaction can mask the true nature of the disturbance and a surgical abdomen dismissed as due to the noted fecal impaction. Carmel reports such a case.

CASE HISTORY

J. W., white male, age 48, entered hospital on September 17, 1951, with history of intermittent rectal pain of two years duration, manifested by bleeding and pain. There had been an increasing constipation of one week's duration with no elimination for two days prior to admission. He had continuous anal pain for two days with swelling at the anal opening. History revealed that the patient had been looking for work in northern Illinois for the past few weeks. The only food eaten in the week prior to admission was tomatoes, cucumbers and melons which he found in the fields. The last three days he ate nothing but wild grapes and elderberries. He estimates that he ate a half-bushel of this material.

Patient was seen by the intern, who referred the patient to the proctology service as a possible bowel malignancy with partial obstruction. Physical examination was negative other than the

proctology findings. Temp. 100, C.B.C. 9/21/51—Hgb. 15 gm. 97% , C.I. 0.98—R.B.C. 4.93—WBC 21,300—Stabs. 13—Segs. 71. T. M. 84—Lymph. 9—Mono. 6—Eosin. 1—Urine: Straw—cloudy—acid 1.025. 2 plus albumin; sugar: 0. Oec. W.B.C./h.p.f.

Patient was seen by the Proctology Service on 9/18/51, at which time he presented an edematous, painful, tender, thrombotic external-internal hemorrhoid in the left lateral position with an edematous papilla on the medial aspect. It was impossible to do a digital examination and hot compresses were advised. The following day it was possible to do a digital examination, which revealed a fecal impaction of rough, gritty material. 15 cc's of novocaine and 5 cc's of Eucupin in oil were injected about the anal opening and by manual extraction approximately a quart of wild grape seeds and elderberry stems were removed. This was followed by a retention enema of:

Fleets Phospho Soda	Oz. II
Water	Oz. IV (Marks)
Hydrogen peroxide	Oz. ss

That evening and the next day the patient spent in the bathroom passing a few seeds at a time. On 9/21/51 a low spinal anesthetic was given and approximately two gallons of the same material was removed by digital maneuver and irrigation with normal saline solution. Following this procedure the patient had marked relief. Subsequently a hemorrhoidectomy and excision of a posterior anal ulcer were done. The patient's convalescence was uneventful and he left the hospital without further complications.

SUMMARY

1. A case of fecal impaction due to wild grape seeds and elderberry stems is presented.
2. The recent American literature on the subject of fecal impaction is reviewed and discussed.

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ABSTRACTS ON NUTRITION

LAWSON, D. F. AND BOLTON, J. H.: *Macrocytic anemia of pregnancy*. Med. J. Australia, Nov. 17, 1951, 669-671.

In their obstetrical practices the authors do rather routine blood examinations and have found that a surprisingly large number of pregnant women show macrocytosis, often with a normal hemoglobin level. Leucopenia is frequently an indication that a macrocytic anemia is present or developing. Such macrocytic anemias do not seem to depend on poverty or ordinary malnutrition. They are associated with fatigue and "neurasthenic" symptoms. They are very promptly cured by the administration of folic acid.

MILLIS, J.: *The iron losses of healthy women during consecutive menstrual cycles*. Med. J. Australia, Dec 29, 1951, 874-879.

The iron losses were determined during consecutive menstrual periods in a group of 14 normal healthy young women, and a pronounced individual variation was shown. The average loss was 21.8 mg. of iron (range 3.2 to 66.8 mg.). The iron losses in a subject varied from one menses to another. The average duration of the cycle was 28.7 days (range 21 to 55 days). A number of women are situated unfavorably for the maintenance of iron equilibrium, and in these women it seems likely that anemia gradually will develop.

HARRIS, L. E.: *Infant feeding with and without added carbohydrate*. Amer. J. Dis. Child., 82, 6, Dec. 1951, 667-684.

Harris is satisfied that formulas prepared with water and fresh whole cow's milk or evaporated cow's milk without additional carbohydrate are quite satisfactory for infant feeding. Gains in weight were the same as for those using carbohydrate, there was less tendency to hard stools, and the incidence of "colic" is somewhat less.

BERGER, H.: *Method of increasing sensitivity of glucose tolerance test*. J. A. M. A., 148, 5, Feb. 2, 1952.

The administration of 100 mg. of ACTH prior to a standard glucose tolerance test increased the blood sugar level determinations of a group of siblings of known diabetics, as well as those of the diabetics themselves. Except in two instances, the ACTH did not affect the curves of normal persons without a family history of diabetes. Possibly the method may reveal potential diabetics not discoverable by other means. (Two glucose tolerance tests were done on each individual, the first one without ACTH, while the second test was preceded by 100 mg. of ACTH one hour prior to the test.) After feeding 100 mg. glucose, blood sugar determinations were made every 30 minutes for 3 hours.

HALLAHAN, J. D.: *Symptomatic relief of osteoarthritis and osteoporosis with vitamin B₁₂* (pre-June, 1952

liminary report). Amer. Prac. & Dig. Treat., 3, 1, Jan. 1952, 27-32.

On a weekly dosage of crystalline vitamin B₁₂ of from 50 to 100 micrograms, the 33 cases of osteoarthritis treated all showed marked relief of symptoms. Of twenty of these patients, 7 had obtained 100 percent relief after one week's treatment. By the end of the third week, 16 showed partial relief of symptoms and 14 had complete relief. By continuing the treatment longer than 3 weeks, some patients who had obtained partial relief found 100 percent relief. No toxic effects were noted.

VAN ITALLIE, T. B., LOGAN, W. B., SMYTHE, R. L., GEYER, R. P. AND STARE, F. J.: *Fat emulsions for oral nutrition. IV. Metabolic studies on human subjects*. Metabolism, 1, 1, Jan. 1952, 80-88.

The authors describe metabolic studies on the assimilation and utilization of an oral fat emulsion supplying 4 calories per c.c. (The emulsion used was Upjohn Company's Lipo Mul-oral). 250 to 550 c.c. of the preparation, providing 1,000 to 2,200 calories per day were tolerated by four volunteer subjects. Nitrogen and potassium deficits due to a calorically inadequate diet were abolished by the use of oral fat emulsion as a caloric supplement. The ingested fat was well assimilated. In one subject, oral fat emulsion favored more efficient utilization of marginal amounts of intravenously administered nitrogen. The importance of a high caloric intake in making possible effective utilization of marginal quantities of dietary or parenterally administered nitrogen was again demonstrated. (The palatability of this oral fat preparation seems to be due to the small size of its fat particles, most of which are below 1 μ in diameter).

CREWS, E. R.: *The value of protein in surgery—special emphasis on oral feedings*. Amer. Pract. & Dig. of Treat., 3, 1, Jan. 1952, 13-17.

The author emphasizes the importance of acceptability in oral protein feedings, since so often such drinks are not appetizing. He tested some two dozen high protein preparations, each containing over 30 percent protein for palatability, settling, protein percentage, carbohydrate, fat, and the retail price per pound of protein. He observed that one dry skim milk product which rates high in characteristics essential for high protein supplementation, is approximately one-fourth as expensive as the other commercial products. He does not, however, specify the product.

WOODRUFF, A. W.: *Anemia of pregnancy among Africans in Nigeria*. Brit. Med. J., Dec. 15, 1951, 1415-1423.

Anemia in pregnancy was studied in Ibadan, Nigeria, some 25 cases furnishing the clinical material. A hemolytic element was present and hepatomegaly and splenomegaly were common. Microcytic and hypochromic anemias were the least common, while normo-

cytic and hypo- or normochromic anemias were commonest, with macrocytic anemias in an intermediary position. The termination of pregnancy was the best "treatment," as practically all the cases rapidly recovered after labor. The bone-marrow almost invariably showed a macro-normocytic picture. Liver biopsy showed the liver diffusely fibrosed in many cases and there was fat infiltration in others. A protein-deficient diet seemed to be a prime causal factor. Prior to labor, blood transfusions and high protein diet seemed to be the best form of treatment. It is suggested that the fetal demands for protein may precipitate the disease. Vitamin B₁₂ and folic acid were comparatively ineffective.

CAMPBELL, D. A., HAY, K. M. AND TONKS, E. M.: *An investigation of the salt and water balance in migraine*. Brit. Med. J., Dec. 15, 1951, 1424-1428.

Migraine is a disease which is accompanied by a disturbance in salt and water metabolism. In the pre-migraine phase, especially in the early stages of the attack itself, the blood sodium rises to a high level, while at the same time there is a marked hydration of the blood. The excessive secretion of sodium and chloride which follows a water imbibition test suggests that an abnormal sodium metabolism is present almost continuously. The suggestion is made that these disturbances are due to the disordered functions of the hormones governing salt and water metabolism of the adrenal cortex and posterior pituitary gland, and that in women they are exacerbated by the influence of certain sex hormones.

HOELZEL, A., KOMROWER, G. M. AND WILSON, V. K.: *Amino-aciduria in galactosemia*. Brit. Med. J., Jan. 26, 1952, 194-195.

Two cases of true galactosemia in infants are reported, in both of which there was renal excretion of amino

acids. Withdrawal of milk from the diet cured the galactosemia and greatly reduced the urinary excretion of amino-acids. This amino-aciduria probably represents a "renal" mechanism, and these are the first cases in which it has been reported in association with galactosemia. As compared with the already known amino-acidurias, the present one was characterized by disproportionately large quantities of threonine, methyl histidine, lysine and tyrosine.

RATNER, B. AND UNTRACHT, S.: *Egg allergy in children*. A. J. Dis. Child., 83, 3, March 1952, 309-316.

The authors' previous estimate that only 0.5 percent of the general population and only 5 percent of allergic persons are sufficiently sensitive to egg to warrant special precautions in the administration of chick-embryo-propagated viral and rickettsial vaccines is further corroborated. Individuals may give positive skin tests to egg white without being clinically sensitive to eggs. Young allergic infants show an inordinately high incidence of egg reactivity but this sensitivity wanes with age.

GERRITZEN, F.: *The duration of the action of different insulins*. Brit. Med. J., Feb. 2, 1952, 249-250.

With regular insulin, the blood sugar reaches its lowest point after one hour and returns to its starting point in 8 hours. PZ insulin acts for 18 hours, the lowest point being reached in 5 to 8 hours. Globin insulin has a duration of action of 16 hours, the lowest point being in the first 3 hours. N.P.H. 50 (Lilly) has a duration of action of 11 hours, the lowest point being after 3 hours. The author used normal human subjects, not diabetics. He fed the subjects about 10 gms. carbohydrate every hour during the experiment.

EDITORIALS

KONJETZNY'S THEORY OF THE DEVELOPMENT OF GASTRO-DUODENAL ULCER.

Among many physicians, there may be the impression that the question of the origin of gastric and duodenal ulcer is a closed one. However, among those who have been working in this field for a long time, the question of the genesis and its peculiar appearances has never ceased, and has never been fully explained in all its different aspects.

Therefore, it is a pleasure to see a book that appeared a few years ago, but, due to postwar conditions, has not gotten the widespread recognition it deserves. I am speaking of Konjetzny's book of 1947. Konjetzny, the surgeon and pathologist, is well known to every gastroenterologist, surgeon and pathologist, for he has devoted a lifetime to the study of the gastro-duodenal ulcer and has published more than fifty articles and books on this subject.

Konjetzny emphasized long ago that ulcers cannot be studied on the autopsy table, for the post mortem changes in such delicate tissues as the surface of the

stomach are too obvious. Therefore, he as a surgeon studied resected stomachs immediately after operation,—operations in which the greatest care was taken not to injure the delicate surface of the stomach by rough handling during the surgical proceedings. The specimens were examined immediately after resection so that all the finer structures of the epithelium could be inspected.

Konjetzny's work in conjunction with his friend and pupil Puhl has been published before, but his last book summarizes their findings and discusses them critically, answering the many questions which have been put to the author in many articles, books and discussions at conventions. Therefore, this book gives the answers to most of the questions gastroenterologists and surgeons would wish to ask after reading Konjetzny's findings.

The author discusses the different theories of ulcer, such as the infarct theory the peptic theory and the theory of inflammatory origin. He dismisses the first two and elaborates on the last one. He shows, that every ulcer is preceded by an inflammatory process, a gastritis or

a duodenitis. Many illustrations of resected stomachs and duodenums, accompanied by many photomicroscopic studies of the organs, illustrate his point. Konjetzny found fibrinous exudates in the connecting tissues of the mucosa, immigration of polynuclear leucocytes in the membrane and glandular epithelium of the mucosa, collections of fibrinous leucocytic exudate on the surface of the mucosa, filling of glands with leucocytes, loosening of the connection of the epithelium with distortion of its pattern. Later a discharge of the surface layers can be seen with resulting erosions. At first, only the microscope can spot the changes brought about in the form of erosions of the tips, dimples and sulci from which fibrinous exudations are discharged. From these microscopic changes, deeper and deeper erosions develop later on. Signs for peptic erosions were never observed. Konjetzny proves by many illustrations the gradual development from the finest erosions into deep, chronic ulcers. One objection to his theory is that in chronic ulcers, the mucosa fails to show signs of gastritis. However, the author has proven that in all those cases the microscope always reveals signs of healed gastritis or stages of repair after gastritis. (Umbau-gastritis). It is his opinion that the clinical symptoms of periodical complaints are due to the inflammatory condition of the mucosa and that the "classic ulcer symptoms" are due to the gastro-duodenitis. It is his conviction that this inflammatory process has no relationship to the secretion of the stomach as he never saw or had histological proof that peptic erosions were present. Besides he states that the intact living gastric mucosa cannot be peptically eroded by the gastric juice.

Konjetzny includes studies of inflammatory processes in different parts of the alimentary tract. He considers regional enteritis (B. B. Crohn) also to be an inflammatory condition, in which there is a gradual change from the acute, superficial inflammation to the chronic stage.

As causes for the gastro-duodenitis the author enumerates the following: mechanical, thermic, chemical, and bacteriological damages, which are connected with foods and pharmaceuticals. He emphasizes the damage after low temperatures.

These are only the excerpts of a very interesting book, which includes 93 illustrations of excellent quality. A long bibliography is added, which enhances the value of this publication. Konjetzny and Puhl have done fundamental research in this field and every gastroenterologist and surgeon will be highly interested in his findings, even if he does not fully agree with the author. We too have been impressed, clinically, with the fact that we are able to demonstrate many duodenal ulcers, which do not give any clinical symptoms. If a duodenum is deformed by an ulcer, we are able to demonstrate the changed appearance for many years. In addition, the roentgenological examination is able to show clearly the swollen, tortuous folds, the presence of mucus in the emptying stomach, and the hypersecretion of the stomach in active ulcer cases. These are additional proofs of Konjetzny's findings. How far the question of hyperacidity plays a role as a cause of "peptic" ulcer, which the author refuses to consider important, we do not want to state; however, the clinical evidence does not support the extreme thesis

of the author. We agree that the absolute titrated values of the stomach contents may be only of secondary importance, a view point somewhat theoretical! Other, not known factors play an important part in gastro-duodenal ulcer. Konjetzny's book urges us to restudy the problem of this very common disease.

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INTENSIVE MEDICAL TREATMENT OF PEPTIC ULCER

Rossett, Knox and Stephenson (1), of the Kennedy Hospital in Memphis, Tennessee, recently reported very striking results in peptic ulcer by the faithful application of a Sippy type of treatment. The diet omitted secretagogues such as alcohol, coffee, tea, Coca-Cola, Spur, condiments, meat extractives, seasoning and citrus fruits. Also, the chief roughage foods were omitted. Extremes of temperature in foods were avoided as well as over-distension. All essential nutrients were included, especially 100 to 150 gm. protein daily. In place of citrus fruits, ascorbic acid, 50 mg. daily, was used. Bedrest was required until 5 days had passed without any pain (usually 10 days total) or until niche disappeared radiographically. In uncomplicated cases, a mixture of aluminum hydroxide gel with 1/5 pint by volume of milk of magnesia was used, giving 45 c.c. between meals, 8 p.m., at bedtime, and every 2 hours through 6 a.m. Tincture of belladonna 1.5 c.c. every 6 hours also was employed. Neutralization was determined by siphoning off the fasting juice at 8 a.m. by a large stomach tube with the patient in the prone Trendelenburg position. Antacids were increased to 150 c.c. every 2 hours if necessary to secure neutralization.

The long-term results of this form of treatment are not given, but it seems obvious that the majority of the patients were made very comfortable in about 10 days. Crater healing was usually complete in a month. This treatment produced pain cessation and ulcer healing in 1,288 consecutive cases of uncomplicated ulcer, *without exception*, or the occurrence of a single episode of obstruction, perforation or bleeding while under therapy.

Such a form of treatment unfortunately cannot be strictly duplicated without hospitalization and a trained group of technicians. On the surface, at least, this work by the Memphis physicians appears to compare very favorably with *any* form of treatment ever used. We will await with great interest for a report on a long-time follow-up of end results. Their work should do much to persuade the profession that medical treatment of ulcer has not as yet reached its ultimate.

1. Rossett, N. E., Knox, F. H., and Stephenson, S. L. Jr.: Peptic ulcer: medical care by efficient gastric acid neutralization. *Ann. Int. Med.*, 36, 1, January 1952, 98-109.

BOOK REVIEWS

DIFFERENTIAL DIAGNOSIS OF INTERNAL DISEASES. Hegglin, Piv. Doz. R., Zuerich. A short description for physicians and students. 456 pg., 220 partly colored illustrations, Georg Thieme, publishers, Stuttgart (Grune & Stratton, New York) price \$11.85.

This is an introduction into internal medicine. It is arranged in twenty chapters according to the leading clinical symptoms, with which the physician is confronted, when he is called to the bedside of the patient. These main symptoms are taken and discussed in chapters like: pains in the region of the thorax, dyspnea, status fibrilis, pains in the region of the abdomen, diarrheas, icterus, and unconsciousness. The clinical picture of the common and especially the rarer conditions is described and analyzed, taking the more recent research findings into consideration. Always, the clinical side is emphasized, however, the laboratory studies are extensively used, especially the simpler ones, so that the practitioner has an advantage in using this book. Very interesting are the different types of pneumonia and their roentgenological appearance. In future editions, the author is, probably, going to use more illustrations in the chapter on diarrhea. Tables for the differential diagnosis of certain groups of diseases are clear and concise, giving the salient features at a glance.

This book, written in a clear German, which is easy to read, is especially useful to all students and general practitioners, however, it will also benefit the specialist, when he is confronted with borderline cases. Instead of thumbing through big volumes in other specialties, he has here precise information within a few minutes. Every chapter has a good bibliography. The index is extensive, many cross references are given in the text. The print, as always in the Thieme books, is very good, the illustrations, excellent. We recommend the book highly.

Franz J. Lust.

FOOD AND NUTRITION. E. W. H. Cruickshank, M. D., Williams and Wilkins Co., Baltimore, Md., 1951, \$6.50.

Cruickshank takes an unusually broad view of food and nutrition and in his introduction, after comparing certain Tribes in Kenya, whose food habits differed with respect to the eating of meat, concludes that meat "in moderation is an excellent adjunct to milk, green vegetables and cereals." He believes, however, that to secure all the elements of the proteins necessary for body-building, much more of vegetables than animal protein must be eaten. He rapidly reviews the changes which have occurred in food habits in Britain, and feels that in the past decade a great deal has been learned as to how the benefits of wholesome food can be made available to all. After a study of "world nutrition," he finds it to be a difficult problem,—one requiring good-will and vision on the part of the statesmen of all nations. Next he deals technically with energy requirements, proteins, minerals, vitamins, and then analyzes the nutritional value and availability of

special food items such as bread, milk, butter, fruits and nuts. Dietary planning as well as the preservation of foods is given due consideration. His section on dental caries is interesting, and he feels that a strong hereditary influence is important in this disease. He wisely correlates nutritional problems with social, economic and political problems. The book is recommended as a common-sense approach to the title subject, even though one may differ from the author in a few details.

LES SYNDROMES DOULOUREUX DE LA REGION EPIGASTRIQUE. Rene A. Gutman, (Doctor of Hospitals of Paris). G. Doin & Co., 8 Place de L'Odéon, Paris, 6, 1951.

This remarkable work (the painful diseases of the epigastric region), in 2 volumes, containing almost 2,000 pages, is, according to Prof. Gosset's preface, unique in French publications. We are obliged to Dr. Ole W. Husebye, The University Clinic, Oslo, Norway, for sending these volumes for our library.

The volumes contain almost 1300 half-tone engravings of x-ray films as well as more than 400 schematic drawings. As Prof. Gosset states, it is obvious that Dr. Gutman is not only an experienced clinician but an habitual visitor to the operating room. The volumes deal exhaustively with gastric and duodenal ulcer, gall-bladder disease, diseases of the pancreas, as well as a large number of other conditions such as duodenal stenosis, inflammatory lesions of the stomach, viscerop-tosis, mobile duodenum, appendicitis, liver abnormalities, renal dyspepsia, dyspepsia of cardiac origin, endocrine syndromes, chronic intoxications, nervous indigestion, duodenitis, hemorrhages, allergies, avitaminoses, syphilis, tuberculosis and other conditions too numerous even to enumerate. The illustrations are excellent and profuse. The use of morphine to increase gastric tone during radiography is described. We believe this work will prove extremely valuable to the clinician and also to the radiologist not only because of its meticulous treatment of each subject but because of its exhaustive nature.

EINFÜHRUNG IN DIE RÖNTGENOLOGIE. (Introduction into Roentgenology). Ein Lehrbuch für Aerzte und Studierende von G. F. Haenisch, a.o. Prof., M. D., and H. Holthausen, o.o. Prof., M. D. Mit einem physikalisch-technischen Beitrag von A. Liechti, bearbeitet und ergänzt von Dr. W. Fehr. Cloth. \$14.30. Pp. 521, with 371 illustrations. Georg Thieme Verlag, Stuttgart; agents for U. S. A. Grune & Stratton, Inc., 381 Fourth Avenue, New York 16, 1951.

This book has been written primarily for students and for those physicians who want to familiarize themselves with the fundamentals of roentgenology. The purpose of an elementary introduction to roentgen diagnosis and therapy has been fully accomplished and it is remarkable how well the authors have covered the immense field on some 500 pages, a great part of the space being taken up by excellent illustrations. And

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this reviewer regrets the fact that such a propaedeutic publication did not exist at the time when he began his roentgenologic training because it enables the student to get a broad view and general knowledge of the specialty within a short period, so that he soon can take part in the routine activities of an x-ray department with greater understanding and therefore increased interest. Before the printing of this work the newcomer had to read larger diagnostic and therapeutic volumes, the study of which required much time, so that it was most difficult for him during the first months to follow the many and different activities in the department.

The diagnostic as well as the therapeutic section is divided into a general and a special part, and in accordance with the authors' aim the general parts are extensive and prepare the reader well for the full ap-

preciation of the subsequent special parts. The chapter on the interpretation of the normal roentgenogram is particularly instructive: wrist, skull, hip and knee joints, lumbar spine, and chest are selected as examples for an exact analysis under careful consideration of different projections. As another example I should like to mention the chapter on the biological effects of ionizing radiation with its abundance of essential information. On the other hand, the special parts do not overlook the diagnosis of such conditions as retropharyngeal abscess or the treatment of agranulocytosis.

Due to this thorough coverage of the vast field of roentgen diagnosis and therapy, including physics, the book will be also of interest to experienced radiologists, especially if its value were enhanced by the addition of a bibliography.

F. C. Burghelm.

GENERAL ABSTRACTS OF CURRENT LITERATURE

G. ALBOT, J. TOULET AND G. F. BONNET, (Paris).: *Tests in front and side-view cholecystography*. Arch. mal. app. dig. 40, 11, 1187, Nov. 1951.

The authors have striven to draw more accurate conclusions from the study of the contraction of the gall bladder in the diagnosis of dyskinesia.

Recorded tests by cholecystography using numerous exposures as well as pharmacodynamic substances administered after or at the same time as the Boyden meal, have furnished information theoretically interesting but of no great practical value.

On the other hand, the authors consider that side-view exposures are essential both before and after the Boyden meal. Actually this incidence enables them to form a more exact idea of the morphology and to discover in a much more accurate way the contraction of the gall-bladder and its pathological variations.

Furthermore, they emphasize the importance of dorsal decubitus, in contrast to the more usually adopted procubitus.

Finally, the exact estimate of the gall-bladder's projection surfaces, front and side-view, thanks to the use of tracing paper marked off in millimeters, enables them to estimate exactly, with figures, the rate of evacuation of the gall-bladder.

It is thus possible by this method, to distinguish between two phenomena up till now confused in ordinary cholecystography: on the one hand the efforts of vesicular contraction, and on the other, the action of its evacuation.

The effort of contraction after Boyden's meal is seen in front-view as a raising of the gall-bladder under the edge of the ribs and as a recoil of the spine. But it is especially easy to determine from the side-view by a straightening up of the lower part of the gall-bladder. The large axis of the gall-bladder in profile after Boyden's meal makes a more marked angle with the spine, and this difference in the angle is a sure sign of the contraction of the gall-bladder.

Other indications of contraction may moreover be

shown up on the side-views; for example, a retraction of the entire shadow of the gall-bladder, a roof-shaped angle due to the more marked retraction of the infundibulum, or a mere arc-shaped contraction due to the change in direction of the posterior curve of the shadow of the gall-bladder.

All these signs enable the contraction of the gall-bladder to be affirmed and its intensity to be determined.

Furthermore, the taking of front and side exposures both before and after Boyden's meal enables the volume of the gall-bladder to be calculated easily and consequently exact figures of the evacuation of the gall-bladder to be given.

With the help of these two facts, one is able to distinguish between:

—normal gall-bladders with normal contraction effort (the angle increases 10 degrees), and the action of normal evacuation (60 to 63% in the case of a woman one hour after Boyden's meal)

—cystic or infundibulo-cystic hypertension with a normal or excessive contraction effort.

—hyperkinetic or irritable gall-bladders with very strong contraction and excessive evacuation.

—finally, vesicular hypotension or atony with very slight evacuation, but proportionate to the effort of contraction which is likewise very slight.

In conclusion the authors advocate the taking of 5 exposures as a standard cholecystographic technique: the first in a standing position with compression and the others from the front and side, before, and one hour (in the case of a woman) or one and a half hours (in case of a man) after Boyden's meal. These last four exposures should be taken in dorsal decubitus with a bulb above the front view exposures, and a bulb on the left of the patient for side view exposures.

R. A. GUTMANN, GUY ALBOT, A. TRICARD, MME JACQUELINE DAUD-GUTMANN: *Atrophic gastritis in patches*—(an element in the radiological diagnosis of cancer of the stomach in its incipient stages).

GUY ALBOT, FRANÇOIS MOUTIER, MME NADINE BERNARD, R. LE CANUET. *A case of a patch of sclerous parietal atrophic gastritis.* The French National Society of Gastro-enterology. Meeting of the 9th of July 1951 in the Archives of diseases of the digestive system and nutrition. Tome 40. no. 11. Nov. 51. pp. 1139 to 1152 and 1179 to 1184. figure.

The authors in their constant preoccupation to track down very small cancers in their incipient stages, stress the difficulty of diagnosis in cases of certain benign lesions.

They describe, on the one hand, the appearance of a patch of *atrophic gastritis*—mucous gastritis— and on the other hand, a patch of *parietal gastritis*.

No functional symptom helps to distinguish them from one another. Only detailed study of the radiological findings enables a diagnosis to be made. Even so it is a case of a very delicate diagnosis of a very difficult problem when it comes to taking on the responsibility of ruling out the serious possibility of an incipient epithelioma. In the 6 cases reported, the authors have never ventured to risk missing an incipient cancer by not performing an operation.

However, the characteristics of these lesions distinguish them from those of cancer. In cancer, the stiffening is rigid, the study of the perilesional relief is of capital importance. The folds, *converging towards the lesion*, cease a long way from the outline of the lesser curvature. They are of abnormal appearance and their endings are swollen into club shapes. They are rigid, and this rigidity is in contrast to the mobility of the folds everywhere else.

In cases of gastritis, on the contrary, the fold which is attached to the under surface of the lesion is neither abnormally big nor stunted, does not end in a club shape, and instead of stopping a long way from the lesion, goes so far as to touch the outline of the lesser curvature.

The segmental rigidity is a slight stiffening without the amazing stiffness of neoplastic rigidity. The lesion persists, and may even become extended, but only very slowly—such lesions rarely show the progressive aggravation typical of cancerous lesions of the mucous membrane.

Anatomically, atrophic gastritis in patches is characterized by atrophy of the mucous membrane, in contrast to cancer in which there is a dense sclerous inspissation.

Parietal gastritis is a rare complaint. One of its manifestations is in fibro-muscular atresia of the pre-pyloric antrum (Albot and Magnier) or in plastic limits. Parietal gastritis in patches is another variety of it.

The nosographic position of these conditions is difficult to state precisely. It is not a case of localized atrophic gastritis, resulting from, and as though persisting over, an ulcer scar.

It seems feasible to assume that the atrophic lesion of the mucous membrane is of long standing and that the break in the secondary muscular coat is due to the exulceration of ulcerous gastritis.

The supposition of the existence of a pre-cancerous lesion is worthy of consideration although at the present time it is impossible to settle the question.

It is a case of a localized form of chronic gastritis usually observed in a diffuse form. The 5th observation shows a transition between the extremely localized and diffuse forms.

CRILE, G., JR. AND ROBNETT, A. H.: *Treatment of pharyngo-esophageal diverticulum by inversion of the sac.* Cleveland Clinic Quart., 18, 1, Jan. 1951.

The authors describe the technique of treating pharyngo-esophageal diverticulum by simple inversion. The operation is simple and avoids infection. The invaginated sac atrophies so quickly that after 2 weeks it is difficult to visualize by esophagoscopy. Eleven patients treated by this method have done well.

HOERR, S. O. AND BROWN, C. H.: *Rubber tube in common bile duct for twenty-five years.* Cleveland Clinic Quart., 18, 1, Jan. 1951.

A patient aged 57 was admitted because of chills, fever and mild intermittent abdominal pain. X-ray of the abdomen showed a radio-opaque rubber tube in the region of the right kidney. At operation a calculus-encrusted tube was removed successfully from the dilated common duct. At an operation for cholecystectomy 25 years previously the common duct was inadvertently cut, the tube being inserted to facilitate suturing the wound. For some reason the tube did not pass. Patient made a good recovery from the second operation.

HOLMES, T. W.: *Alarming melena in the presence of non-specific jejunitis.* Alex. Blain Hosp. Bull., 9, 4, Nov. 1950.

Cases of gastrointestinal hemorrhage due to bizarre causes are discussed and several inciting lesions incriminated. A case is reported in which exsanguinating melena was apparently produced by a non-specific inflammatory process restricted to the upper small intestine and in which the process subsided promptly after exploratory laparotomy, without further interference. Only one other similar report was found in the literature, (Stone, H. B. "Alarming melena of obscure origin," Trans. Am. Surg. Assoc., 62, 582, 1944).

GUTCH, C. F.: *The treatment of amebiasis, with a preliminary report on the use of aureomycin.* Ann. Int. Med., 33, 6, 1407-1412, Dec. 1951.

Treatment of amebiasis by a combination of emetine, carbarsone and the iodine-containing oxyquinoline derivatives has a significant failure rate, and produces toxic symptoms which may be easily overlooked. 35 patients had serial EKGs while receiving emetine, and 37 percent showed abnormal tracings, and in 8 percent changes were persistent after 6 weeks. In a series of 20 cases, results from aureomycin compared favorably with other amebicidal agents in relief of symptoms and prompt elimination of parasites from the stool. It is considered a desirable agent for the treatment of amebiasis because of the absence of serious toxic action.

SINCLAIR, W. J.: *Ligneous cecitis*. Alex. Blain Hosp. Bull., 9, 4, Nov. 1950.

The author describes two cases of ligneous cecitis and explains that the wood-like condition of the cecum is due to marked fibrous tissue reaction and subdued or attenuated inflammatory reaction. It usually occurs in elderly persons in whom the local circulation is impaired and results from perforation of a retrocecal appendix. X-ray may indicate distorted outlines of the lateral walls of the cecum. The treatment advocated is partial colectomy because of the danger of infection and concealed malignancy. The differential diagnosis from cancer of the cecum is clinically difficult or impossible.

HALLIGAN, E. J., PERKEL, L. L. AND CATLAW, J. K.: *Surgical treatment of carcinoma of the colon and rectum*. Am. J. Proctology, 1, 4, Dec. 1950.

The authors advocate wider resection of cancer of the colon, especially the left half, and rectum. In the past 10 years resectability is higher and death rate lower and 5-year survivals more frequent. Unfortunately, early diagnosis has not advanced as rapidly as antibiotics and operative management. A one-stage abdominoperineal resection should be done for all lesions below 15 cms. from the anal margin.

DERRICK, E. H. AND BROWN, H. E.: *A survey of human brucellosis in Queensland*. Med. J. Australia, 11, 20, Nov. 11, 1950.

The authors report 25 cases of brucellosis in Queensland, occurring over a period of 14 years. Diagnosis was made by the agglutination test, confirmed in one case by the isolation of a strain of *Brucella suis*. Association with cattle or pigs offers a much higher risk of brucellar infection in Queensland than the ingestion of milk. Probably *Brucella melitensis* is not present in Australia. *Brucella suis* is more invasive for man than *B. abortus*. The symptoms of these cases described were fever, chills, malaise, headache, loss of weight and generalized pains and anorexia. Two patients were treated with chloromycetin with good results.

PRIESTLY, J. T., WALTERS, W., GRAY, H. K. AND WAUGH, J. M.: *Annual report on surgery of the biliary system and pancreas for 1949*. Proc. Staff Meet. Mayo Clin., 25, 25, Dec. 1950.

The mortality rate in 1659 cases undergoing surgery on the biliary system and pancreas in 1949 was 0.9 percent,—lower than in previous years. Factors causing this improved mortality rate were—more accurate preoperative diagnosis, better evaluation and preparation of patients, more effective means for combatting infection, greater attention to the prevention of post-operative pulmonary and thrombo-embolic complications, more accurate control of the water, electrolyte and nutritional requirements of seriously ill patients and more emphasis on the prevention rather than the treatment of post-operative complications.

BASNUEVO, J. G., CHAVEZ, O. C. AND ARJORA, A. D.: *Chloroquine in the treatment of intestinal ulcerations due to E. histolytica*. Revista KUBA de Med. Trop., 6, 5 and 6, June 1950.

The authors report a case of amebiasis treated with

chloroquine in which the amebae disappeared from the stools and the intestinal ulcers healed, but two weeks later the amebae returned and blood appeared in the feces. Like emetine, chloroquine is not very effective in intestinal amebiasis. Although chloroquine is much better than emetine in treating hepatic abscess, it is inferior to diiodohydroxyquinoline in treating intestinal amebiasis.

SHARPE, M. AND GOLDEN, R.: *End-to-end anastomosis of the colon following resection*. Am. J. Roentg. and Rad. Ther., 64, 5, Nov. 1950.

Forty-four cases of resection of the colon with end-to-end anastomosis were studied by barium enema from a few weeks to seven years after operation. A short bilateral constriction was found in the majority of cases. Such constriction probably is due to a structural change in the wall resulting from the anastomosis.

NICHOLS, G. B.: *The prone position in the roentgenological diagnosis of free intra-abdominal gas*. Am. J. Roentg. and Rad. Ther., 64, 5, Nov. 1950.

The rupture of a hollow viscus can be determined by the presence of free intra-abdominal gas in 80 percent of the cases. The prone or supine films show an area of decreased density in the liver shadow at the outer border of the right kidney, or between the spleen and the left kidney, or the spleen and the diaphragm.

UNGER, L. AND UNGER, A. H.: *A new (sublingual) method for controlling the pain of migraine and other headaches*. Illinois Med. J., 99, 4, 210-211, Apr. 1951.

The authors believe migraine to be a food allergy, curable if the offending substance can be avoided. For attacks of migraine they have found a 5 grain tablet of aspirin sweetened with saccharine to be extremely effective if dissolved under the tongue, thus permitting rapid absorption. (Such a tablet is made by the Church Chemical Corporation, Chicago).

JONES, H. H., KAPLAN, H. S. AND WINDHOLZ, F.: *Air-contrast colon examination with colloidal barium*. Radiology, 54, 6, 561-566, April 1951.

The authors describe a modified double-contrast method of examination of the colon for the demonstration of polypoid lesions. A special colloidal barium preparation is used for the enema, followed by the introduction of air. Spot films are then made with the patient in various positions. (The nature of the colloidal barium preparation was described in California Med.: 74: 155-160, March 1951). The reproductions of films are very beautiful and clear.

GOTTLIEB, C., DORFMAN, M. AND CREGG, H.: *Pancreatitis: its preoperative diagnosis by gastrointestinal roentgenography*. Radiology, 56, 4, 528-534, Apr. 1951.

Nine cases of pancreatic enlargement due to pancreatitis are presented. All of these showed indirect roentgen signs of pancreatic disease, due in most instances to encroachment of the enlarged pancreas on the duodenum. While a specific diagnosis cannot be made solely on the roentgen findings, attention to these indirect signs will permit a more positive approach to the diagnosis of pancreatic lesions.

SANDWEISS, D. J.: *Physiological principles underlying treatment of peptic ulcer*. Harper Hosp. Bull., 9, 2, 41-56, Mar.-Apr. 1951.

The cause of peptic ulcer is unknown but a major element of treatment is the neutralization, inhibition or elimination of hydrochloric acid, which when successful renders the patient symptom-free, though not necessarily cured. In medical treatment, frequent small feedings of foods that bind acid and stimulate the enterogastrone mechanism are advocated. Foods that mechanically irritate or stimulate the gastrin and secretagogue mechanisms are withheld. Antacids, drugs to inhibit secretion and motility by subduing the vagi, as well as sedatives, are employed. In the surgical treatment, gastroenterostomy reduces acidity by reason of alkaline regurgitation; subtotal gastrectomy removes the gastrin mechanism thus appreciably reducing acid secretion. A true acidity is not produced, however. Vagotomy aims at eliminating the psychic phase of gastric secretion and reducing motor activity but both of these tend to return to normal levels months after vagotomy.

GORDON, W. H. AND KASTON, H. A.: *Islet cell tumor of the pancreas*. Harper Hosp. Bull., 9, 2, 60-63, Mar.-Apr. 1951.

The authors made a diagnosis of islet cell tumor of the pancreas on a man of 50 because of the finding of blood sugar levels of less than 50 mg. per 100 c.c. of blood on many occasions while fasting and also following acute episodes of weakness, sweating and syncope. He was always improved temporarily by glucose administration, but refused surgical exploration. Chronic asthma, from which he suffered, disappeared following the institution of a high protein, high carbohydrate diet with interval feedings,—a regime which likewise controlled his hypoglycemic symptoms. He had a failing rheumatic heart and this factor brought about his death. (Cortisone was used for a few days terminally to combat the asthma and the authors surmise that adrenal exhaustion may have been an adverse factor). Post-mortem examination revealed an adenoma of the pancreas 3 c.m. in diameter.

STEWART, IAN S. AND THOMSON, G. RUSSELL. *Argentaffin tumor of the ileum with perforation*. British Med. J. p. 1316. Dec. 1, 1951.

A case of perforation of the small intestine resulting

from one of three argentaffin tumors of the ileum is described. Treatment was by excision of all three, restoration of the continuity of the gut, and closure of the abdomen without drainage after liberal application of sulphanilamide powder to the operation sites. The patient recovered uneventfully. No roentgenologic studies are reported. No mass could be palpated on abdominal examination, but during vaginal examination, a hard tender mass was felt above the right fornix.

Franz J. Lust.

THOMAS, S. F., HENRY, G. W. AND KAPLAN, H. S.: *Hepatolienography: past, present and future*. Radiology, 57, 5, Nov. 1951, 669-684.

The authors emphasize the fact that after the use of thorotrast (colloidal thorium dioxide) serious late fibrosis and scar formation may occur either in the liver and spleen or in sites of accidental extravascular injection. This result is frequent enough to constitute a justifiable contraindication to the use of thorium dioxide for any diagnostic procedures except in cases of extreme urgency or where life expectancy is short. The use of the ethyl ester of the tri-iodide of stearic acid ("Jodsol") and of the brominated fatty acids for demonstration of the liver and spleen, as reported in the German and Swedish literature, is cited. Original studies are reported on the use of inorganic metallic compounds such as tantalum and iodized oil emulsions stabilized with new types of wetting agents.

BROWN, C. H. AND CHOISSER, R. V.: *Obstructive biliary cirrhosis with ascites*. Cleveland Clinic Quart., 18, 4, Oct. 1951, 251-259.

The authors present two unusual cases of obstructive biliary cirrhosis with ascites. In the first case, the cirrhosis and ascites were secondary to a common duct stone and cure followed removal of the stone. The second case was due to stricture of the common duct and illustrates the often relentless course and fatal termination in these patients despite repeated attempts at reconstruction of the common duct and re-establishment of biliary drainage. Both cases, incidentally, demonstrate the severe changes in the liver that can result from obstruction of the extrahepatic bile ducts.

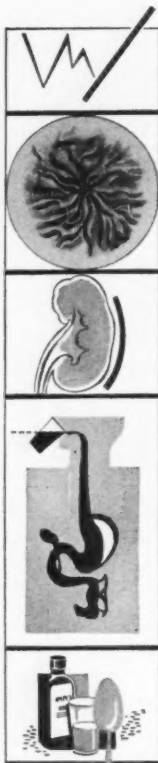
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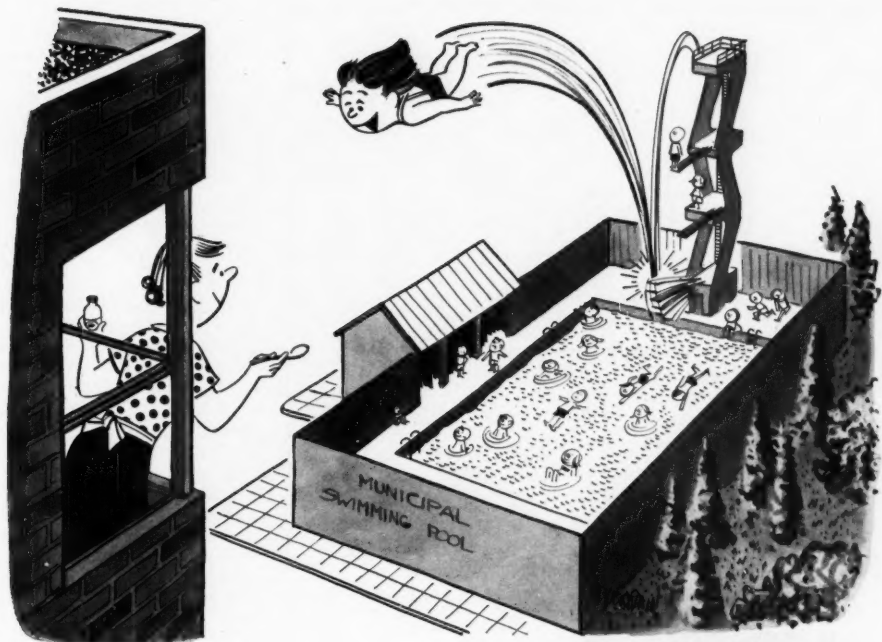
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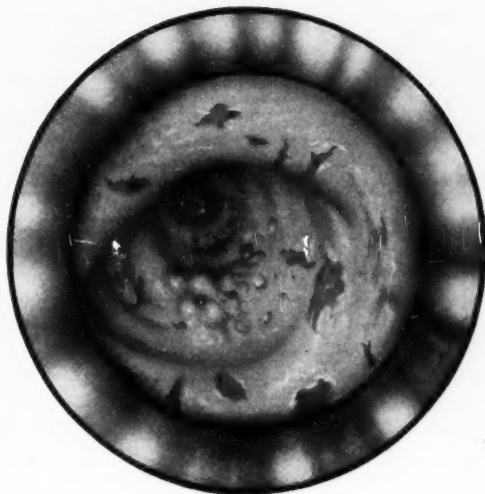
One complete session will be devoted to a Clinical Pathological Conference at the Mt. Sinai Hospital in New York City.

For further information and enrollment write to the National Gastroenterological Association, Department GSJ, 1819 Broadway, New York 23, N. Y.

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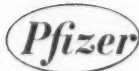
1. Dowling, H. F., et al.: *Ann. New York Acad. Sc.* 53:433 (Sept. 15) 1950.

2. Sayer, R. J., et al.: *Am. J. M. Sc.* 221:256 (March) 1951.

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Comprising the reports published in the literature to date which give specific facts and figures of the results of treatment

AUTHORS	No. of Patients	Chronic, Resistant to Other Therapy	TYPES OF ULCERS				RELIEF OF SYMPTOMS (Chiefly Pain)				Surgery or Complications ¹	Side Effects Requiring Discontinuance of Drug ²	EVIDENCE OF HEALING			
			Duodenal	Jejunal	Stomal	Gastric	Good	Fair	Poor	No Report			Complete	Moderate	None	No Report
Grimson, Lyons, Reeves	100	100	93	7			80	11	4		5		47		19	29
Friedman	15	15	14			1	5		4	6 ³			2			13
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TOTALS	1443	968	1380	17	8	38	1142	132	131	12	26	54	552	52	179	634
PERCENTAGES		67.8	95.6	1.2	0.6	2.6	81.3	9.4	9.3			3.7	70.5	6.6	22.9	

1. Not included in tabulations.

2. Included in "Relief of Symptoms" as "Poor" and in "Evidence of Healing" as "None."

3. Four had no symptoms when Banthine therapy was begun.

4. Of which seven were penetrative lesions and five partially obstructive.

5. No symptoms were present in four.

6. Two with symptoms only; no demonstrable ulcer.

7. Three were psychopathic patients and one had a ventricular ulcer of the lesser curvature.

8. Roentgen findings after treatment period of two weeks; forty-seven had duodenal deformity.

9. All returned to work within a week.

10. In these four, after relief of symptoms, Banthine was discontinued because of urinary retention.

During the past two years, more than 200 references to Banthine therapy in peptic ulcer and other parasympathotonic conditions have appeared in medical literature. Of these reports, 22 have presented specific facts and figures on the results of treatment in a total of 1,443 peptic ulcer patients, 67.8 per cent of whom were reported as chronic or resistant to other therapy. These results are tabulated above and show:

"Good" relief of symptoms was obtained in 81.3 per cent of the 1,405 patients on whom reports were available.

"Complete" evidence of healing was obtained in 70.5 per cent of the 883 patients on whom reports were available.

In all but 9.7 per cent, relief of pain was "good" or "fair." In all but 22.9 per cent, evidence of healing was "complete" or "moderate."

During treatment, 26 patients required surgery or developed complications other than ulcer which required discontinuance of the drug before results could be evaluated.

Of the remaining 1,417 patients, only 3.7 per cent experienced side effects sufficiently annoying to require discontinuance of the drug.



*Volume containing complete references, with abstracts of 39 additional reports, will be furnished on request by

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